Changes in anthropometric and blood 25-hydroxyvitamin D measurements in antenatal vitamin supplemented gestational diabetes mellitus patients: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective: Gestation weight (GW), body mass index (BMI), and blood 25-hydroxyvitamin D [25(OH)D] level during pregnancy are important determinants of the gestational outcomes. This study aimed to study how these parameters vary between antenatal vitamin D recipients and non-recipients in gestational diabetes mellitus (GDM) patients.

Material and Methods: The randomized controlled trials comparing these outcomes between vitamin D recipient and non-recipient GDM patients were searched in electronic databases (PubMed, Embase, and Scopus). The reviewed studies’ data were abstracted and critically appraised using the Cochrane tool. The estimation of the weighted mean difference for GW and BMI and standardized mean difference (SMD) for 25(OH)D levels occurred by juxtaposing the interventions meta-analytically (random-effect model). The statistical inconsistency was determined by Chi² and I² method. The statistical significance was estimated at p<0.05 and 95% confidence interval (CI).

Results: Eleven eligible trials (all Iran-based, except one), sourcing data from about 875 GDM patients, were reviewed. Overall, the risk of bias was low, except for selection and performance bias. On random-effect model meta-analysis, the 25(OH)D levels of the GDM patients favored the vitamin D recipients when compared to non-vitamin D (SMD 1.97, 95% CI: 1.06-2.88, p<0.001; I² 96.2%, p of Chi² <0.001) and placebo (SMD 1.86, 95% CI: 0.95-2.77, p<0.001; I² 95.3%, p of Chi² <0.001) recipients, respectively. On meta-regression, sample size was a predictor of the observed heterogeneity. For GW and BMI the interventions did not differ statistically significantly.

Conclusion: In GDM patients, antenatal use of vitamin D aids in the rise of blood 25(OH)D levels. However, vitamin D supplementation did not affect change in GW or BMI. (J Turk Ger Gynecol Assoc 2021; 22: 217-34)

Keywords: Gestational diabetes, vitamin D, dietary supplement

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Introduction

Gestational diabetes mellitus (GDM) refers to any degree of glucose intolerance that develops or is identified initially during gestation (1). Its global prevalence is about 7-10% (2-5). GDM diagnosis is made using glucose challenge tests between 24-28 weeks of gestation (1). Initial GDM management encompasses diet and exercise therapy, but if these fail to achieve glycemic control, physicians start insulin therapy (1).

GDM is a crucial health burden since it can affect both the GDM patient and her neonate. Gestational weight (GW)
and body mass index (BMI) in pregnancy are two important anthropometric determinants of GDM-related outcomes. Studies in GDM patients suggest that an excessive GW accumulation increases the risk of maternal complications, such as increased likelihood of cesarean delivery, large for gestational age, and gestational hypertension and fetal problems, such as macrosomia, large for gestational age, hypoglycemia in newborns, and poor APGAR score (6-11). It remains unclear if the Institute of Medicine’s guideline (2009) for recommended GW gain for respective BMI categories can be applied to the GDM subpopulation or not (8,12). However, studies on overweight and obese GDM patients found that gaining GW less than that recommended for their respective BMI categories resulted in favorable obstetric and neonatal outcomes (8,13,14). Maintaining an optimum weight before and during pregnancy, therefore, can decrease the complications of pregnancy (9). Nevertheless, it remains unclear if any antenatal intervention in GDM patients may be beneficial in achieving an acceptable GW and BMI.

In this respect, vitamin D has emerged as a potentially useful agent that has attracted attention. In GDM patients, various clinical trials (15-18) have tested the maternal health effect of antenatal vitamin D supplementation, and due to the different relationships between GDM and vitamin D status in the body, such testing appears pertinent. For instance, inadequate vitamin D levels in the body are associated with an increased risk of developing GDM (19-23). Vitamin D deficiency (<20 ng/mL) has a nearly fourfold increased risk of GDM development than women with sufficient vitamin D level (>30 ng/mL) after adjusting for the age of the mother, race, ethnicity, and family history of type 2 diabetes among first-degree family members (24). Moreover, studies showed a decreased GDM prevalence in prenatal vitamin D recipients (25,26). Given this evidence it is important to understand how vitamin D supplementation in GDM mothers can affect GW and their BMI. Additionally, as the fetus entirely depends on maternal 25-hydroxyvitamin D [25(OH)D] levels, maternal levels in GDM mothers after vitamin D supplementation also requires evaluation (27).

**Intervention description**

The inactive forms of the fat-soluble vitamin D are D2 (ergocalciferol) and D3 (cholecalciferol) (28,29). Both forms are available from diet and supplements and vitamin D3 is also produced in the skin on exposure to sunlight (28,29). On hydroxylation of pre-vitamin D in the liver, the main circulating form, 25(OH)D, of vitamin D is produced (27). In blood, 25(OH)D is either present in the bound form (to albumin) or free form (27). For its physiologic role, it is converted to the active form, calcitriol 1,25-dihydroxyvitamin D (28,30). The physiological effect of Vitamin D in pregnancy is mediated via calcitriol’s action on the vitamin D receptors in uteroplacental tissue (28,30). Compared to calcitriol, which has a half-life of 4-6 hours (27), the relatively longer half-life of 25(OH)D of between two and three weeks (31) makes the latter an ideal marker for vitamin D status (32).

In GDM patients, contemporary trials have supplemented vitamin D at various dosages. For oral preparations, while some trials used it at a dose of 50,000 IU, two to three weeks apart for three to eight weeks (33-36), other trials used it twice daily at 200-500 IU for six to sixteen weeks (17,37). One trial used a single intramuscular injection of vitamin D at a dose of 300,000 IU (38). Furthermore, while few trials used the vitamin as a single supplement (33,37,38), others co-supplemented it with various micronutrients, including zinc, magnesium, and calcium (17,34).

**What this review adds?**

In contemporary medicine, several clinical trials have tested the changes in GW, BMI, and plasma 25(OH)D level in GDM mothers, after antenatal vitamin D supplementation (15,34-36). Recent reviews have studied the effect of antenatal vitamin D supplementation on certain maternal complications such as cesarean section rate, pre-eclampsia, preterm delivery, macrosomia, and polyhydramnios and/or on neonatal complications including hyperbilirubinemia, hypoglycemia, and hospitalization (39-41). However, to the best of our knowledge, there is no systematic review and meta-analysis that studied how maternal GW, BMI, and 25(OH)D levels change in the blood on vitamin D supplementation in GDM patients. Therefore, this study explores this under-reviewed area of modern medicine by a systematic literature search, critical appraisal, and meta-analysis.

**Aims**

This study compared the GW, BMI, and 25(OH)D levels among vitamin D supplemented and not-supplemented GDM patients.

**Material and Methods**

This systematic review is registered in the PROSPERO database (CRD42020149613) and has a pre-published protocol (42,43). This report adheres to the PRISMA 2009 reporting guideline (Supplement Table 1) (44).

**Inclusion criteria**

1. **Study design:** Parallel arm randomized controlled trials of any number of intervention arms.
2. **Population:** Pregnant females of any age were eligible, irrespective of their pre-pregnancy BMI and 25(OH)D levels.
They must be diagnosed with GDM during their concurrent pregnancy.

3. Intervention arm: The treatment arm/s should have received vitamin D as a sole or co-supplement.

4. Comparator arm: The comparator arm/s may have received a placebo or any other supplement except vitamin D. Comparator arm/s not receiving any intervention were also eligible.

5. Outcomes: The trials must report the GW (kg), BMI (kg/m²), and 25(OH)D (in ng/mL or mmol/L) in the above GDM patients before and after receiving these interventions and before childbirth.

We accepted the diagnosis and management of GDM and the dosage and regimen of interventions received by the participants in the respective treatment arms as per the trialists.

Exclusion criteria
1. Study design other than those described above, e.g., observational studies and crossover studies.
2. Participants with diabetes types besides GDM, like type 1 or type 2 diabetes.
3. Studies conducted on animals.
4. Editorials, abstracts from conference presentations (where a full published manuscript is not available), letters, or any other brief communications.

Database search
We searched the title and abstract of prospective trials matching the above eligibility criteria in PubMed, Embase, and Scopus databases, irrespective of the date and language of publication and geographical boundary. The following search terms were used “vitamin D” OR “calciferol” OR “vitamin D2” OR “ergocalciferol” OR “vitamin D3” OR “cholecalciferol” AND “GDM” OR “gestational diabetes” along with these MeSH terms- “Cholecalciferol”, “ergocalciferols”, and “diabetes, gestational”. To identify the clinical trials in PubMed [(Clinical Trial) and (Randomized Controlled Trial)] and Embase [(controlled clinical trial) and (randomized controlled trial)], we used filters. In Scopus, instead of filters, the following search terms were used: “trial,” “randomised,” “randomized,” and “controlled.” The last date of the search was 17 September, 2020. Additionally, we reviewed the references of the papers included in this review.

We uploaded the retrieved citations (from database search) in the Rayyan systematic review software (45) and eliminated the duplicate articles. Successively, skimming of the remaining citations’ titles and abstracts against the eligibility criteria commenced. Articles were read in full-text when it seemed to meet the inclusion criteria, or if the suitability for incorporation in this review was doubtful.

Data abstraction and risk of bias assessment
We extracted data about the study design, consent, ethics, registration number of the trial, participant features, interventions contrasted, and the outcomes of interest in a pre-piloted form. With the Cochrane collaboration tool, individual trial’s risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and any other bias was determined, and each of these risk of bias (RoB) components was categorized as low, high, or unclear (46). To assess selection bias, the random allocation sequence generation method, and its concealment method from participants, were judged. The blinding mechanism of study participants and personnel and that of outcome assessors were used to evaluate the performance and detection bias, respectively. By evaluating missing outcome data, and its reason among the intervention arms, the risk of attrition bias, was evaluated. Any additional bias, besides the above, comprised the other bias type. For a visual presentation of the RoB, we prepared an RoB graph and an RoB summary using the Review Manager (RevMan) software (46,47).

The review authors independently performed study selection, data abstraction, and RoB assessment, and resolved any disagreement in an opinion by discourse.

Meta-analysis
The juxtaposed interventions’ effect on each of the outcomes was contrasted by random-effects meta-analysis (using DerSimonian and Laird method) since we assumed clinical heterogeneity among the trials attributable to the different types of vitamin D co-supplements used in these. The use of endpoint means of the respective outcomes and their SDs ensued to conduct the meta-analysis. We estimated the meta-analytic effect sizes of GW and BMI in weighted mean differences (WMD) and that of 25(OH)D levels in standardized mean differences (SMD) due to the identical and non-identical types of measuring units used in the trials, respectively. A decrease in the summary effect of GW and BMI, and its increase in 25(OH)D levels, denoted a favorable meta-analytic finding. For any outcome, when multiple treatment arms tested an intervention, the post-intervention means and their SDs of those intervention groups were combined for meta-analysis (46). Outcome reported in the median were not considered for meta-analysis.

Heterogeneity and meta-regression
The statistical heterogeneity was determined by Chi² (statistically significant at p<0.1) and F (categorized as low,
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moderate, and high at I² values of 25, 50, and 75%, respectively) statistics (48). To account for any substantial heterogeneity, we performed univariate meta-regression by presence or absence of missing outcome data and sample size (categorized as <100 and ≥100). Using the predictor identified by meta-regression, we did a subgroup analysis to see how heterogeneity changed across the different categories of the predictor.

Publication bias and sensitivity analysis

The publication bias assessment incorporated visual inspection of funnel plots and Egger’s test. For each outcome, a sensitivity analysis included iteration of the meta-analysis using a fixed-effect model and by dropping a trial each time.

Statistical analysis

Using random-effect and fixed-effect models, all outcomes were compared meta-analytically between vitamin D and placebo-receiving GDM patients.

We estimated the statistical significance of meta-analysis derived effect sizes at p<0.05 and 95% confidence interval (CI). Stata statistical software v16 (StataCorp, College Station, TX) was used for analysis.

Results

Scope of the review

The database search retrieved 271 citations. After eliminating the duplicates, 188 citations underwent skimming against the eligibility criteria. Out of the 22 articles needing full-text reading, 11 trials sourcing data from about 875 participants published between 2014-19, were included in this review (15-18,33-35,37,49,50). All trials except the Chinese one (37) were Iran-based, and the average age of participants in the respective intervention arms was approximately 28-32 years. The intervention period of Iranian (16-18,33,49,50) and Chinese (37) trials were 6-8 and 16 weeks, respectively. In most trials (15-18,33,37,49,50), GDM was diagnosed primarily using the American Diabetes Association criteria (52,53). Insulin was not used during the intervention period, except in the trial by Yazdchi et al. (33). Eight trials (15,16,18,33,34,37,49,50) used the D3 form of the vitamin while this was not clear among the remaining trials (17,35,51). In most of the trials (81.8%), a co-supplement (e.g., calcium, magnesium, zinc, omega-3 fatty acid, evening primrose oil, probiotic) accompanied the vitamin D supplementation (15-18,34,35,37,50,51). The intervention was given between 24-28 weeks of gestation in nine trials (15-18,33,35,49,50), at 16 weeks of gestation in one trial (37), and in the remaining one, this was unclear (51). Table 1 depicts the salient features of the trials.

RoB assessment

In most studies, the allocation concealment component of the selection bias and performance bias was unclear (Table 2 and Figure 2). Otherwise, the RoB was low.

Meta-analysis findings

Eleven trials comparing GW (15,16,51,17,18,33-35,37,49,50), and 10 trials contrasting BMI (15-18,33-35,49-51) with one study (37) excluded as it did not report the follow up BMI, and 25(OH)D with one trial (33) excluded for reporting follow up value in median, were included in the meta-analytic juxtaposition between vitamin D recipients and its non-recipients. The antenatal vitamin D use in GDM patients favored plasma 25(OH)D level attainment compared to its non-supplementation (random-effect model: SMD 1.97, 95% CI: 1.06-2.88, p<0.001; I² 96.2%, p of Chi² <0.001). The post-intervention GW (random-effect model: WMD 0.18, 95% CI, -1.10-1.47, p=0.773; F 0%, p of Chi² 0.559) and BMI (random-effect model: WMD 0.27, 95% CI, -0.28-0.82, p=0.331; F 0%, p of Chi² 0.838) were not statistically significantly different between the juxtaposed interventions (Figure 3).

Meta-regression and subgroup analysis

The univariate meta-regression suggested that sample size was a statistically significant predictor of the observed heterogeneity in the effect size of 25(OH)D level (Supplement Table 2). Upon subgroup analysis by the sample size, heterogeneity was moderate when sample size was ≥100, and the effect size increased (random-effect model: SMD 3.81, p<0.001; 95% CI, 3.03-4.59; F 72.5%) (Supplement Figure 1).

Publications bias

For 25(OH)D, a small study effect was suggested by the asymmetric funnel plots (Supplement Figure 2) and Egger’s test (p=0.005). On trim-and-fill analysis, no additional study was imputed. Funnel plots for the rest of the outcomes were approximately symmetric.

Sensitivity analysis

On using a fixed-effect model meta-analysis, the summary estimate of 25(OH)D level, reduced slightly (SMD 1.74, 95% CI, 1.57-1.92, p<0.001). The fixed-effect meta-analysis results for the rest of the outcomes were identical to the preliminary analysis. The meta-analysis findings for all outcomes remained unchanged on dropping a study each time and repeating the meta-analysis.

Supplementary meta-analysis

Between vitamin D and placebo, ten trials (15-18,33,35,49-51) compared GW and BMI, and nine trials (15-18,34,35,49-50,51) compared GW and 25(OH)D.
51) juxtaposed 25(OH)D levels, with one study (33) excluded because the study reported 25(OH)D values as medians. Vitamin D recipients achieved a favorable blood 25(OH)D level compared to the placebo recipients (random-effect model: SMD 1.86, 95% CI, 0.95-2.77, p<0.001; I², 95.36%, p of Chi² <0.001) (Figure 4). The effect size of 25(OH)D levels reduced slightly on using a fixed-effect meta-analysis model (SMD 1.45, 95% CI, 1.25-1.64). GW and BMI, when contrasted among the intervention arms, were not statistically significantly different. Since <10 studies were available for the 25(OH)D levels, we did not explore heterogeneity or assess the publication bias for it.

**Discussion**

Overall, 11 trials, mostly Iranian, tested the effect of antenatal vitamin D complementation (as a co-supplement primarily) on GW, BMI, and 25(OH)D in 875 GDM patients, were retrieved. The intervention favored a rise in blood 25(OH)D levels, and the sample size was the plausible predictor of the observed heterogeneity.

**Evidence quality**

Utilizing the GRADE Working Group’s (2004) (54) approach of grading evidence quality we graded the evidence concerning the 25(OH)D level as of moderate-quality, due to the unclear RoB components and heterogeneity.

**Comparison with what is known**

As the context remains underexplored in contemporary literature, a direct juxtaposition of our findings to existing reviews is not possible. However, clinical trials studying the effect of vitamin D supplementation on 25(OH)D level in pregnant females with no glucose intolerance are available for a contrast. Two such trials found that vitamin D supplementation in the third trimester increased maternal plasma 25(OH)D levels compared to the control group (55,56). Another randomized trial found that vitamin D supplementation caused a statistically significantly greater increase in the 25(OH)D level than the placebo (57). Mirroring these trials’ findings (55-57), we observed that vitamin D3 supplementation in GDM patients increased the maternal 25(OH)D level.

![Figure 1. Study selection process [PRISMA flow chart (58)]](image-url)
# Table 1. Summary table

| Trial                        | Design                                      | Population                                                                 | Intervention arms                                                                                     | Outcomes reported                      |
|------------------------------|---------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------|
| Karamali et al. (16)         | Randomized, placebo-controlled trial        | Diagnosis: GDM (using ADA criteria)                                        | Calcium and vitamin D arm: calcium carbonate 1000 mg/day (six weeks) and 50,000 IU D3 (at trial initiation and 21st day). Placebo arm. Intervention given between 24 and 28 weeks of pregnancy. Total vitamin D received in six weeks: 100,000 IU. |
|                              | Blinding: double blinded                    | Number of participants randomized: 60                                     |                                                                                                        | 1. GW                                   |
|                              | Number of intervention arms: two            | Calcium and vitamin D arm (n): 30                                          |                                                                                                        | 2. BMI                                  |
|                              | Multi-center or single-center trial: multi-centric | Placebo group (n): 30                                                      |                                                                                                        | 3. 25(OH)D                             |
|                              | Study duration: six weeks                   | Average age of Calcium and vitamin D arm: 28.7 (6.1) years                 |                                                                                                        |                                        |
|                              | Country where trial was conducted: Iran     | Average age of placebo group: 31.6 (6.3) years                             |                                                                                                        |                                        |
|                              | Ethical permission: obtained                | Missing outcome data: 0                                                    |                                                                                                        |                                        |
|                              | Consent from participants: obtained         | Baseline mean BMI (SD): Placebo group: 30.5 (4.5) kg/m²; Calcium and vitamin D arm: 29.4 (4.7) kg/m² |                                                                                                        |                                        |
|                              | Information regarding funding: provided     | Baseline mean GW (SD): Placebo group: 78.1 (13.4) kg; Calcium and vitamin D arm: 73.7 (12.8) kg |                                                                                                        |                                        |
|                              | Clinical trial registration number:         | Baseline mean (SD) vitamin D levels: Placebo group: 20.8 (14.4) ng/mL; Calcium and vitamin D arm: 17.3 (10.9) ng/mL |                                                                                                        |                                        |
|                              | IRCT201407115623N23                        |                                                                                                        |                                                                                                        |                                        |
| Karamali et al. (17)         | Randomized placebo-controlled trial         | Diagnosis: GDM (using ADA criteria)                                        | Magnesium, calcium, zinc and vitamin D arm: 100 mg magnesium, 400 mg calcium, 4 mg zinc, and 200 IU vitamin D 2x/d (six weeks). Placebo arm. Total vitamin D received in six weeks: 16,800 IU. |
|                              | Blinding: double blinded                    | Number of participants randomized: 60                                     |                                                                                                        | 1. GW                                   |
|                              | Number of intervention arms: two            | Magnesium, zinc, calcium and vitamin D supplements arm (n): 30             |                                                                                                        | 2. BMI                                  |
|                              | Multi-center or single-center trial: single-centric | Placebo group (n): 30                                                      |                                                                                                        | 3. 25(OH)D                             |
|                              | Study duration: six weeks                   | Average age of magnesium, zinc, calcium and vitamin D supplements arm: 30 (4.5) years |                                                                                                        |                                        |
|                              | Country where trial was conducted: Iran     | Average age of placebo group: 31.1 (4.2) years                             |                                                                                                        |                                        |
|                              | Ethical permission: obtained                | Missing outcome data: 0                                                    |                                                                                                        |                                        |
|                              | Consent from participants: not clear        | Baseline mean BMI (SD): Placebo group: 27 (2.6) kg/m²; Magnesium, zinc, calcium and vitamin D supplements arm: 27.4 (4.8) kg/m² |                                                                                                        |                                        |
|                              | Information regarding funding: provided     | Baseline mean GW (SD): Placebo group: 70.7 (7.2) kg; Magnesium, zinc, calcium and vitamin D supplements arm: 70.9 (12.8) kg |                                                                                                        |                                        |
|                              | Clinical trial registration number:         | Baseline mean (SD) vitamin D levels: Placebo group: 20.21 (10.73) ng/mL; Magnesium, zinc, calcium and vitamin D supplements arm: 18.96 (11.23) ng/mL |                                                                                                        |                                        |
|                              | not available                               |                                                                                                        |                                                                                                        |                                        |
| Asemi et al. (49)            | Randomized, placebo-controlled trial        | Diagnosis: GDM (using ADA criteria)                                        | Vitamin D arm: 50,000 IU D3 (at trial initiation and 21st day). Placebo arm. Total vitamin D received in six weeks: 100,000 IU. |
|                              | Blinding: double blinded                    | Number of participants randomized: 50                                     |                                                                                                        | 1. GW                                   |
|                              | Number of intervention arms: two            | Vitamin D arm (n): 25                                                      |                                                                                                        | 2. BMI                                  |
|                              | Multi-center or single-center trial: multi-centric | Placebo group (n): 25                                                      |                                                                                                        | 3. 25(OH)D                             |
|                              | Study duration: six weeks                   | Average age of vitamin D arm: 31.1 (5.5) years                             |                                                                                                        |                                        |
|                              | Country where trial was conducted: Iran     | Average age of placebo group: 30.8 (6.2) years                             |                                                                                                        |                                        |
|                              | Ethical permission: obtained                | Missing outcome data: 5 (three in vitamin D arm and two in placebo group): Causes of missingness: intra-uterine fetal death (n=1), placenta abruption (n=1), completed bed rest (n=1), insulin therapy (n=1), pre-eclampsia (n=1) |                                                                                                        |                                        |
|                              | Consent from participants: obtained         | Baseline mean BMI (SD): Placebo group: 30.5 (4.5) kg/m²; Vitamin D arm: 30.7 (3.9) kg/m² |                                                                                                        |                                        |
|                              | Information regarding funding: provided     | Baseline mean GW (SD): Placebo group: 77.8 (12.9) kg; Vitamin D arm: 79.0 (9.7) kg |                                                                                                        |                                        |
|                              | Clinical trial registration number:         | Baseline mean (SD) vitamin D levels: Placebo group: 20.9 (14.3) ng/mL; Vitamin D arm: 18.9 (14.5) ng/mL |                                                                                                        |                                        |
|                              | IRCT201305115623N7                         |                                                                                                        |                                                                                                        |                                        |
### Table 1. Continued

| Trial                      | Design                                                                 | Population                                      | Intervention arms                                                                 | Outcomes reported                                                                 |
|----------------------------|------------------------------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| **Jamilian et al. (50)**   | Randomized, placebo-controlled trial                                   | Diagnosis: GDM (using ADA criteria)              | Probiotic and vitamin D arm: 50,000 IU D3 (every 2 weeks) and $8 \times 10^9$ CFU/g probiotic | 1. GW 2. BMI 3. 25(OH)D                                                         |
|                            | Blinding: double blinded                                               | Number of participants randomized: 90           | Probiotic arm: $8 \times 10^9$ CFU/g probiotic                                     |                                                                                  |
|                            | No. of treatment arms: two                                             | Probiotic arm (n): 30                           | Placebo arm.                                                                      |                                                                                  |
|                            | Single centered trial                                                 | Placebo group (n): 30                           | Total vitamin D received in six weeks: 150,000 IU                                  |                                                                                  |
|                            | Study duration: six weeks                                              | Average age of probiotic and vitamin D arm: 28.9 (6.1) years |                                                                                  |                                                                                  |
|                            | Country where trial was conducted: Iran                               | Average age of probiotic group: 31.2 (5.9) years |                                                                                  |                                                                                  |
|                            | Ethical permission: obtained                                           | Average age of placebo group: 29.9 (3.7) years   |                                                                                  |                                                                                  |
|                            | Consent from participants: obtained                                   | Missing outcome data: 3                        |                                                                                  |                                                                                  |
|                            | Information regarding funding: provided                               | Causes of missingness: insulin therapy (n=1) and hospitalization (n=1) |                                                                                  |                                                                                  |
|                            | Clinical trial registration number: IRCT201706075623N119               | Baseline mean BMI (SD): Placebo group: 27.5 (3.3) kg/m² |                                                                                  |                                                                                  |
|                            |                                                                        | Probiotic and vitamin D arm: 27.8 (4.9) kg/m²    |                                                                                  |                                                                                  |
|                            |                                                                        | Probiotic group: 26.4 (4.2) kg/m²               |                                                                                  |                                                                                  |
| **Jamilian et al. (18)**   | Randomized, placebo-controlled trial                                   | Diagnosis: GDM (using ADA criteria)              | Magnesium, calcium, zinc, and vitamin D arm: 100 mg magnesium, 400 mg calcium, 4 mg zinc, and 200 IU D3: | 1. GW 2. BMI 3. 25(OH)D                                                         |
|                            | Blinding: double blinded                                               | Number of participants randomized: 60           | two times daily for six weeks. Placebo arm.                                      |                                                                                  |
|                            | No. of treatment arms: two                                             | Magnesium, zinc, calcium plus vitamin D arm: 25.3 (2.5) kg/m² | Total vitamin D received in six weeks: 16800 IU                                  |                                                                                  |
|                            | Single centered trial                                                 | Placebo group (n): 30                           |                                                                                  |                                                                                  |
|                            | Study duration: six weeks                                              | Average age of magnesium, zinc, calcium plus vitamin D arm: 25.8 (3.7) kg/m² |                                                                                  |                                                                                  |
|                            | Country where trial was conducted: Iran                               | Baseline mean BMI (SD): Placebo group: 25.3 (3.3) kg/m² |                                                                                  |                                                                                  |
|                            | Ethical permission: obtained                                           | Baseline mean GW (SD): Placebo group: 72.0 (7.7) kg |                                                                                  |                                                                                  |
|                            | Consent from participants: obtained                                   | Probiotic and vitamin D arm: 71.9 (12.1) kg      |                                                                                  |                                                                                  |
|                            | Information regarding funding: provided                               | Probiotic group: 70.0 (12.5) kg                 |                                                                                  |                                                                                  |
|                            | Clinical trial registration number: IRCT201704225623N109               | Baseline mean (SD) vitamin D levels: Placebo group: 14.3 (4.1) ng/mL, Probiotic and vitamin D arm: 13.4 (4.1) ng/mL; Probiotic group: 12.9 (3.2 ng/mL) |                                                                                  |                                                                                  |
| **Li and Xing (37)**       | Randomized, clinical trial                                            | Diagnosis: GDM (using ADA criteria)              | Magnesium, calcium, zinc, and vitamin D arm: 100 mg magnesium, 400 mg calcium, 4 mg zinc, and 200 IU D3: | 1. GW 2. BMI 3. 25(OH)D                                                         |
|                            | Blinding: double blinded                                               | Number of participants randomized: 103          | two times daily for six weeks. Placebo arm.                                      |                                                                                  |
|                            | No of treatment arms: two                                             | Yoghurt supplemented with vitamin D arm (n): 52  | Total vitamin D received in six weeks: 112,000 IU                                  |                                                                                  |
|                            | Multicentric trial                                                    | Plain yoghurt group (n): 51                     |                                                                                  |                                                                                  |
|                            | Study duration: 16 weeks                                              | Average age of yoghurt supplemented with vitamin D arm: 29.0 ± 5.3 years |                                                                                  |                                                                                  |
|                            | Country where trial was conducted: China                              | Average age of plain yoghurt group: 28.3 ± 4.1 years |                                                                                  |                                                                                  |
|                            | Ethical permission: obtained                                           | Missing outcome data: 6                        |                                                                                  |                                                                                  |
|                            | Consent from participants: obtained                                   | Baseline mean GW (SD): Plain yoghurt group 69.3 ± 6.7 kg; Yoghurt supplemented with vitamin D arm: 67.9 ± 7.1 kg |                                                                                  |                                                                                  |
|                            | Information regarding funding: not clear                              | Baseline mean (SD) vitamin D levels: Plain yoghurt group: 16.2 (3.4) ng/mL, Yoghurt supplemented with vitamin D arm: 16.8 ± 4.6 ng/mL |                                                                                  |                                                                                  |
|                            | Clinical trial registration number: not clear                           | Total vitamin D received in six weeks: 500 IU D3 |                                                                                  |                                                                                  |
|                            |                                                                        | (twice daily for 16 weeks). Plain yoghurt arm: twice daily for 16 weeks. |                                                                                  |                                                                                  |
| Trial                  | Design                                      | Population                                                                 | Intervention arms                                                                 | Outcomes reported               |
|-----------------------|---------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------|
| Razavi et al. (51)    | Randomized clinical trial                   | Diagnosis: GDM (using ADA criteria)                                         | Vitamin D arm: 50,000 IU (two weekly)                                             | 1. GW                          |
|                       | Blinding: double blinded                     | Number of participants randomized: 120                                     | Omega-3 arm: 1,000 mg omega-3 fatty acids two times a day                         | 2. BMI                         |
|                       | No. of treatment arms: two                  | Vitamin D arm (n): 30                                                       | Vitamin D and Omega-3 arm: 50,000 IU (two weekly) and 1,000 mg omega-3 fatty acids two times a day | 3. 25(OH)D                    |
|                       | Single centered trial                       | Omega-3 arm (n): 30                                                        | Placebo arm.                                                                       |                                |
|                       | (59)                                         | Placebo arm (n): 30                                                         | Total vitamin D received in six weeks: 150,000 IU                                  |                                |
|                       | Study duration: six weeks.                  | Average age of Vitamin D arm: 29.9±5.0 years                                |                                                                                  |                                |
|                       | Country where trial was conducted: Iran     | Average age of Omega-3 arm: 29.7±3.6 years                                  |                                                                                  |                                |
|                       | Ethical permission: obtained                | Average age of vitamin D and Omega-3 arm: 29.9±4.0 years                    |                                                                                  |                                |
|                       | Consent from participants: obtained         | Average age of placebo arm: 29.2±3.4 years                                  |                                                                                  |                                |
|                       | Information regarding funding: provided     | Missing outcome data: 0                                                     |                                                                                  |                                |
|                       | Clinical trial registration number:         | Base line mean GW (SD): Vitamin D arm: 76.1±12.7 kg                        |                                                                                  |                                |
|                       | IRTCT201701305623N106                       | Omega-3 arm: 74.3±5.8 kg; vitamin D and Omega-3 arm: 77.4±10.2 kg; Placebo arm: 75.1±7.7 kg |                                                                                  |                                |
|                       |                                               | Study duration: 6 weeks.                                                    |                                                                                  |                                |
|                       |                                               | Country where trial was conducted: Iran                                     |                                                                                  |                                |
|                       |                                               | Ethical permission: obtained                                                |                                                                                  |                                |
|                       |                                               | Consent from participants: obtained                                         |                                                                                  |                                |
|                       |                                               | Information regarding funding: provided                                    |                                                                                  |                                |
|                       |                                               | Clinical trial registration number: IRTCT201701305623N106                    |                                                                                  |                                |
| Yazdchi et al. (33)   | Randomized controlled clinical trial        | Diagnosis: GDM (using International Association of Diabetes and Pregnancy Study Groups criteria) | Vitamin D arm: 50,000 IU D3 (two weekly)                                           | 1. GW                          |
|                       | Blinding: double blinded                     | Number of participants randomized: 76                                      | Placebo arm.                                                                       | 2. BMI                         |
|                       | No. of treatment arms: two                  | Vitamin D arm (n): 38                                                       | Total vitamin D received in eight weeks: 200,000 IU                                 | 3. 25(OH)D                    |
|                       | Single centered trial                       | Placebo arm (n): 38                                                         |                                                                                  |                                |
|                       | (8)                                         | Average age of Vitamin D arm: 31.64±4.40 years                              |                                                                                  |                                |
|                       | Study duration: 8 weeks.                    | Average age of placebo arm: 32.11±3.61 years                                |                                                                                  |                                |
|                       | Country where trial was conducted: Iran     | Missing outcome data: 4 (severe preeclampsia (1), early childbirth (1), unwilling to continue (1), and hospitalization (1)) |                                                                                  |                                |
|                       | Ethical permission: obtained                | Base line mean GW (SD): Vitamin D arm: 81.48±10.79 kg; Placebo arm: 81.09±9.80 kg |                                                                                  |                                |
|                       | Consent from participants: obtained         | Base line mean (SD) BMI: Vitamin D arm: 31.51±3.74 kg/m²; Placebo arm: 31.47±3.71 kg/m² |                                                                                  |                                |
|                       | Information regarding funding: provided     | Vitamin D levels data was reported in median (25th and 75th percentiles) due to non-parametric distribution: |                                                                                  |                                |
|                       | Clinical trial registration number:         | Base line mean (SD) 25(OH)D: Vitamin D arm: 9.54 (6.12-15.94) ng/mL; Placebo arm: 9.02 (7.29-14.70) ng/mL |                                                                                  |                                |
|                       | IRTCT201306253140N11                        |                                                                                  |                                                                                  |                                |
| Asemi et al. (34)     | Randomized clinical trial                   | Diagnosis: GDM (using ADA criteria)                                         | Vitamin D and calcium arm: 1,000 mg calcium carbonate (daily) and 50,000 U D3 (at trial initiation and on 21st day) | 1. GW                          |
|                       | Blinding: double blinded                     | Number of participants randomized: 56                                      | Placebo arm.                                                                       | 2. BMI                         |
|                       | No. of treatment arms: two                  | Vitamin D and calcium arm (n): 28                                           | Total vitamin D received in six weeks: 100,000 IU                                  | 3. 25(OH)D                    |
|                       | Multicentric trial                          | Placebo arm (n): 28                                                         |                                                                                  |                                |
|                       | Study duration: six weeks.                  | Average age of vitamin D and calcium arm: 28.7±6.0 years                    |                                                                                  |                                |
|                       | Country where trial was conducted: Iran     | Average age of placebo arm: 30.8±6.6 years                                  |                                                                                  |                                |
|                       | Ethical permission: obtained                | Missing outcome data: 5                                                      |                                                                                  |                                |
|                       | Consent from participants: obtained         | Base line mean (SD) GW: Vitamin D and calcium arm: 73.6±13.0 kg; Placebo arm: 78.2±13.6 kg |                                                                                  |                                |
|                       | Information regarding funding: provided     | Base line mean (SD) BMI: Vitamin D and calcium arm: 29.4±4.6 kg/m²; Placebo arm: 30.5±4.6 kg/m² |                                                                                  |                                |
|                       | Clinical trial registration number:         | Base line mean (SD) 25(OH)D: Vitamin D and calcium arm: 43.11±28.17 nmol/L; Placebo arm: 49.05±34.30 nmol/L |                                                                                  |                                |
|                       | IRTCT201311205623N11                        |                                                                                  |                                                                                  |                                |
### Table 1. Continued

| Trial                        | Design                                      | Population                                                                                                                                  | Intervention arms                                      | Outcomes reported                                      |
|------------------------------|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|
| Jamilian et al. (15)         | Randomized placebo-controlled clinical trial | Diagnosis: GDM (using ADA criteria) Number of participants randomized: 60 Vitamin D3 and EPO arm (n): 30 Placebo arm (n): 30 Average age of vitamin D3 and EPO arm: 28.4±6.2 years Average age of placebo arm: 29.6±4.3 years Missing outcome data: 6 (all withdrawn from the trial due to personal reasons) Baseline mean (SD) GW: Vitamin D3 and EPO arm: 71.5±10.8 kg; placebo arm: 72.3±8.5 kg Baseline mean (SD) BMI: Vitamin D3 and EPO arm: 27.0±4.2 kg/m²; placebo arm: 27.6±3.5 kg/m² Baseline mean (SD) 25(OH)D: Vitamin D3 and EPO arm: 14.0±10.1 ng/mL; placebo arm: 11.4±4.3 ng/mL | Vitamin D3 and EPO arm: 1,000 IU of vitamin D and 1,000 mg of EPO: daily (60) Placebo arm. Total vitamin D received in six weeks: 42,000 IU. | 1. GW 2. BMI 3. 25(OH)D |
| Jamilian et al. (35)         | Randomized, placebo-controlled clinical trial | Diagnosis: GDM (using ADA criteria) Number of participants randomized: 140 Vitamin D and omega-3 fatty acid arm (n): 35 Vitamin D arm (n): 35 Omega-3 fatty acid arm (n): 35 Placebo arm (n): 35 Average age of vitamin D and omega-3 fatty acid arm: 31.2±4.3 years Average age of vitamin D arm: 31.5±7.0 years Average age of omega-3 arm: 30.7±3.5 years Average age of placebo arm: 30.7±4.1 years Missing outcome data: 6 (all withdrawn from the trial due to personal reasons) Baseline mean (SD) GW: Vitamin D and omega-3 fatty acid arm: 77.3±9.9 kg Vitamin D arm: 78.4±15.2 kg Omega-3 fatty acid arm: 75.0±5.8 kg Placebo arm: 75.9±7.1 kg Baseline mean (SD) BMI: Vitamin D and omega-3 fatty acid arm: 29.7±3.9 kg/m² Vitamin D arm: 29.7±5.1 kg/m² Omega-3 fatty acid arm: 28.8±2.4 kg/m² Placebo arm: 29.2±3.4 kg/m² Baseline mean (SD) 25(OH)D: Vitamin D and omega-3 fatty acid arm: 15.5±3.1 ng/mL; vitamin D arm: 15.2±3.8 ng/mL; Omega-3 fatty acid arm: 16.9±3.5 ng/mL; placebo arm: 16.6±2.6 ng/mL | Vitamin D and omega-3 fatty acid arm: 50,000 IU of vitamin D (two weekly) and 1000 mg omega-3 fatty acid (twice daily) Vitamin D arm: 50000 IU vitamin D (two weekly) Omega-3 fatty acid arm: 1000 mg omega-3 fatty acids Placebo arm. | 1. GW 2. BMI 3. 25(OH)D |

ADA: American Diabetes Association (52,53); EPO: evening primrose oil, GDM: Gestational diabetes mellitus, BMI: Body mass index, SD: Standard deviation, GW: Gestation weight, 25(OH)D: 25-hydroxyvitamin D
Implications and strengths
The chief inference of this paper is that it informs about the rigor of the current evidence of the maternal benefits of prenatal vitamin D supplementation in GDM patients. From the perspective of maternal health, this study may help health authorities to determine if large scale supplementation for all GDM pregnancies will be an appropriate public health initiative or not, given the current evidence. Moreover, as the reviewed trials were primarily Iran-based, this paper might encourage

Table 2. Risk of bias assessment

| Trial*       | Selection bias (Random sequence generation) | Selection bias (Allocation concealment) | Performance bias Outcome: BMI, GW, and 25(OH)2D | Detection bias Outcome: BMI, GW, and 25(OH)2D | Attrition bias | Reporting bias | Other bias |
|--------------|---------------------------------------------|----------------------------------------|-----------------------------------------------|-----------------------------------------------|---------------|---------------|------------|
| Karamali et al. (16) | Low | Unclear | Unclear | Low | Low | Low | Low |
| Karamali et al. (17) | Low | Unclear | Unclear | Low | Low | Low | Low |
| Asemi et al. (49) | Low | Unclear | Unclear | Low | Low | Low | Low |
| Jamilian et al. (50) | Low | Low | Unclear | Low | Low | Low | Low |
| Jamilian et al. (18) | Low | Low | Unclear | Low | Low | Low | Low |
| Li and Xing (37) | Low | Unclear | Unclear | Low | Low | Low | Low |
| Razavi et al. (51) | Low | Low | Low | Low | Low | Low | Low |
| Yazdchi et al. (33) | Low | Unclear | Unclear | Low | Low | Low | Low |
| Asemi et al. (34) | Low | Low | Low | Low | Low | Low | Low |
| Jamilian et al. (35) | Low | Unclear | Unclear | Low | Low | Low | Low |

Authors’ comment: Allocation concealment: it’s not clear if the midwife who measured did the random allocation of participant (in an unblind manner) was related the study personnel or the outcome assessor; Performance bias: Participants were blinded by making the placebos identical to the supplements. However, it’s not clear if study personnel were adequately blinded or not.

Authors’ comment: Allocation concealment: Precise mechanism not clear; Performance bias: Participants were blinded by making the placebos identical to the supplements. However, it’s not clear if study personnel were adequately blinded or not.

Authors’ comment: Allocation concealment: Precise mechanism not clear; Performance bias: Participants were blinded by making the placebos identical to the supplements. However, it’s not clear if study personnel were adequately blinded or not.

Authors’ comment: Allocation concealment: Precise mechanism not clear; Performance bias: Participants were blinded by making the placebos identical to the supplements. However, it’s not clear if study personnel were adequately blinded or not.

Authors’ comment: Allocation concealment: Precise mechanism not clear; Performance bias: Participants were blinded by making the placebos identical to the supplements. However, it’s not clear if study personnel were adequately blinded or not.

Authors’ comment: Allocation concealment: Precise mechanism not clear; Performance bias: Participants were blinded by making the placebos identical to the supplements. However, it’s not clear if study personnel were adequately blinded or not.

Authors’ comment: It remains unclear if the midwife responsible for random sequence generation and its allocation concealment was also the study personnel or anyway could have broken the blinding of the study personnel.

*1st author’s last name and publication year.
BMI: Body mass index, 25(OH)2D: 1,25-dihydroxyvitamin D, GW: Gestation weight
future trialists to conduct identical trials globally to generate generalizable evidence. Concerning the strength, this systematic review is one of the preliminary efforts to investigate the maternal effects of antenatal vitamin D supplementation in GDM patients. A further strength was the unbound nature of our electronic database search to include any date, language, or geographical boundary, thus adding comprehensiveness to our review. Finally, evidence generated from this systematic review and meta-analysis is likely to be rigorous, as it’s grounded on the highest level of epidemiological evidence, randomized controlled trials.

Despite these strengths, this paper has a few weaknesses. As most trials were conducted in Iran, the external validity of this review is likely to be compromised. The heterogeneity observed for the 25(OH)D levels might have increased the risk of bias in our estimates, and this can be because one of the studies was not from Iran. Besides, the maternal health effects of vitamin D supplementation remains inseparable from other supplements that were simultaneously given to the participants in most trials.

**Conclusion**

Using vitamin D as the chief ingredient of antenatal supplements favors in blood 25(OH)D level rise in GDM patients. However, the effect of these supplements on GW and BMI was not distinguishable from those subjects who did not receive supplementation.
Figure 3. Forest plots depicting meta-analysis findings (random-effect model). Outcome: gestational weight a), body mass index b), and 25(OH)D level in blood c). A comparison between antenatal vitamin D supplementation (as the only or co-supplement with other supplements) and non-vitamin D based supplementation; Two trials had with identical trial author name and year have been suffixed with alphabet “a” (50) and “b” (18) after the study name and year.

SD: Standard deviation, CI: Confidence interval, SMD: Standardized mean difference, 25(OH)D: 25-hydroxyvitamin D
| Outcome: Gestational weight | Vitamin D | Placebo | WMD with 95% CI | Weight (%) |
|-----------------------------|-----------|---------|----------------|------------|
| Study                       | N Mean SD | N Mean SD |                |            |
| Asemi et al. (34) (2014)    | 28 75.5 13.2 28 79.9 13.3 | | -4.40 (-11.34, 2.54) | 5.33 |
| Asemi et al. (49) (2015)    | 22 60.5 9.8 23 79.5 12.5 | | 1.00 (-5.58, 7.56) | 5.93 |
| Jamilian et al. (15) (2016) | 30 73.6 10.7 30 74.4 8.5 | | -0.80 (-5.69, 4.09) | 10.74 |
| Jamilian et al. (35) (2017) | 70 80.5 12.5 73 77.9 7.8 | | 2.15 (-2.40, 6.70) | 12.39 |
| Jamilian et al. (50) (2019a)| 30 73.6 12.1 28 73.8 7.7 | | -0.20 (-5.46, 5.06) | 9.28 |
| Jamilian et al. (18) (2019b)| 30 70 9.2 30 69.4 6.1 | | 0.60 (-3.35, 4.55) | 16.46 |
| Karamali et al. (16) (2016)| 30 75.6 12.9 30 80.1 13 | | -4.50 (-11.05, 2.05) | 5.98 |
| Karamali et al. (17) (2016)| 30 72.5 12.6 30 72.3 7.1 | | 0.20 (-4.98, 5.38) | 9.59 |
| Razavi et al. (51) (2017)  | 60 79.3 11.25 30 77.5 7.7 | | 1.80 (-2.66, 6.28) | 12.81 |
| Yazdchi et al. (33) (2016) | 36 85.9 10.53 36 85.7 9.93 | | 0.20 (-4.53, 4.93) | 11.49 |

Overall

Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00

Test of θ = 0; z = 0.11, p = 0.91

Random-effects DerSimonian-Laird model

| Outcome: Body mass index | Vitamin D | Placebo | WMD with 95% CI | Weight (%) |
|--------------------------|-----------|---------|----------------|------------|
| Study                    | N Mean SD | N Mean SD |                |            |
| Asemi et al. (34) (2014) | 28 30.2 4.7 28 31.2 4.5 | | -1.00 (-3.41, 1.41) | 6.36 |
| Asemi et al. (49) (2015) | 22 31.2 4.2 23 31.1 4.3 | | 0.10 (-2.33, 2.53) | 6.26 |
| Jamilian et al. (15) (2016)| 30 27.7 4.3 30 28.4 3.3 | | -0.70 (-2.61, 1.21) | 10.12 |
| Jamilian et al. (35) (2017)| 70 30.5 4.45 35 29.9 3.4 | | 0.60 (-1.08, 2.28) | 13.14 |
| Jamilian et al. (50) (2019a)| 30 28.5 4.9 28 28.2 3.3 | | 0.30 (-1.87, 2.47) | 7.88 |
| Jamilian et al. (18) (2019b)| 30 26.4 4.7 30 26 2.6 | | 0.40 (-1.19, 1.99) | 14.64 |
| Karamali et al. (16) (2016)| 30 30.2 4.7 30 31.2 4.4 | | -1.00 (-3.30, 1.30) | 6.96 |
| Karamali et al. (17) (2018)| 30 28 4.7 30 27.6 2.6 | | 0.40 (-1.52, 2.32) | 10.00 |
| Razavi et al. (51) (2017)| 60 30.3 4.25 30 29.7 3.4 | | 0.60 (-1.15, 2.35) | 12.09 |
| Yazdchi et al. (33) (2016)| 36 33.24 3.63 36 33.28 3.8 | | -0.04 (-1.76, 1.68) | 12.54 |

Overall

Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00

Test of θ = 0; z = 0.23, p = 0.82

Random-effects DerSimonian-Laird model

| Outcome: Blood 25(OH)D level | Vitamin D | Placebo | SMD with 95% CI | Weight (%) |
|-------------------------------|-----------|---------|----------------|------------|
| Study                        | N Mean SD | N Mean SD |                |            |
| Asemi et al. (34) (2014)    | 28 91.3 54.6 28 50.8 35.48 | | 0.87 (0.33, 1.41) | 11.26 |
| Asemi et al. (49) (2015)    | 22 40.4 27 23 21.5 14.8 | | 0.86 (0.26, 1.46) | 11.16 |
| Jamilian et al. (15) (2016)| 30 20.9 10.3 30 11.3 4.7 | | 1.18 (0.34, 1.73) | 11.26 |
| Jamilian et al. (35) (2017)| 70 35.75 5.3 35 16.5 2.6 | | 4.17 (3.47, 4.86) | 10.99 |
| Jamilian et al. (50) (2019a)| 30 35.1 3.9 28 17.7 3.7 | | 4.51 (3.55, 5.48) | 10.37 |
| Jamilian et al. (18) (2019b)| 30 18.7 4.7 30 17.3 3.1 | | 0.35 (-0.16, 0.85) | 11.33 |
| Karamali et al. (16) (2016)| 30 36.3 21.3 30 21.3 14.4 | | 0.81 (0.29, 1.33) | 11.30 |
| Karamali et al. (17) (2018)| 30 32.44 16.72 30 20.71 11.23 | | 0.81 (0.29, 1.33) | 11.30 |
| Razavi et al. (51) (2017)| 60 32.75 5.65 30 14.7 3.2 | | 3.49 (2.82, 4.16) | 11.03 |

Overall

Heterogeneity: τ² = 1.85, I² = 95.36%, H² = 21.54

Test of θ = 0; z = 2.99, p = 0.00

Random-effects DerSimonian-Laird model

Figure 4. Forest plots depicting meta-analysis findings (random-effect model). Outcome: gestational weight a), body mass index b), and 25(OH)D level in blood c). A comparison between antenatal vitamin D supplementation (as a sole or co-supplement with other supplements) and placebo; Two trials had with identical trial author name and year have been suffixed with alphabet “a” (50) and “b” (18) after the study name and year

SD: Standard deviation, CI: Confidence interval, SMD: Standardized mean difference, 25(OH)D: 25-hydroxyvitamin D
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## Supplement Table 1. PRISMA checklist

| Section/topic                  | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|-------------------------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| **Title**                     | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                              | 1                 |
| **Abstract**                  |   |                                                                                                                                                                                                               |                   |
| Structured summary            | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3               |
| **Introduction**              |   |                                                                                                                                                                                                               |                   |
| Rationale                     | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                   | 4-6               |
| Objectives                    | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                 | 6                 |
| **Methods**                   |   |                                                                                                                                                                                                               |                   |
| Protocol and registration     | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                             | 6                 |
| Eligibility criteria          | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                        | 7                 |
| Information sources           | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                             | 7                 |
| Search                        | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                       | 7-8               |
| Study selection               | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                  | 8                 |
| Data collection process       | 10| Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                               | 8                 |
| Data items                    | 11| List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                             | 8                 |
| Risk of bias in individual studies | 12| Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.             | 8-9               |
| Summary measures              | 13| State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                   | 9                 |
| Synthesis of results          | 14| Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., F) for each meta-analysis.                                                           | 9                 |
| Risk of bias across studies   | 15| Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                                    | 10                |
| Additional analyses           | 16| Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                  | 10                |
| **Results**                   |   |                                                                                                                                                                                                               |                   |
| Study selection               | 17| Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                   | 10                |
| Study characteristics         | 18| For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                     | 10-11             |
| Risk of bias within studies   | 19| Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                       | 11                |
| Results of individual studies | 20| For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.       | 12                |
| Synthesis of results          | 21| Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                          | 11-12             |
| Risk of bias across studies   | 22| Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                                  | 11-12             |
## Supplement Table 1. Continued

| Section/topic          | #  | Checklist item                                                                 | Reported on page # |
|------------------------|----|-------------------------------------------------------------------------------|--------------------|
| Results                | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 11-12              |
| Discussion             | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 13                 |
| Limitations            | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 14                 |
| Conclusions            | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 14                 |

### From: Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.

### Supplement Figure 1. Forest plot showing meta-analysis comparing between antenatal vitamin D supplementation (as a sole or co-supplement with other supplements) and non-vitamin D supplementation results on 25(OH)D level in blood using random-effect model. Subgroup by sample size (<100 and ≥100 category); Two trials have identical trial author name and year that have been suffixed with alphabet “a” (61) and “b” (27) after the study year

**SD:** Standard deviation, **CI:** Confidence interval, **SMD:** Standardized mean difference, **25(OH)D:** 25-hydroxyvitamin D
Supplement Table 2. Univariate meta-regression analysis

| Category            | Univariate model | p-value | 95% CI  |
|---------------------|------------------|---------|---------|
|                     | Univariate model |         |         |
|                     | Estimate         | p-value | 95% CI  |
| Participant attrition| No               | 1       | -       |
|                     | Yes              | 1.05    | 0.308   | -0.97, 3.07 |
| Sample size         | <100             | 1       | -       |
|                     | ≥100             | 2.31    | 0.028*  | 0.25, 4.37 |

*p<0.05, CI: Confidence interval

Supplement Figure 2. Funnel plot assessing publication bias between vitamin D supplemented and not supplemented GDM mothers for 25(OH)D levels in the blood

GDM: Gestational diabetes mellitus, SMD: Standardized mean difference, CI: Confidence interval, 25(OH)D: 25-hydroxyvitamin D