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Original Article

The risk of morbidities in newborns of antenatal vitamin D supplemented gestational diabetes mellitus patients

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ABSTRACT

Background: There is no established antenatal intervention that reduces the risk of preeclampsia and preterm delivery in gestational diabetes mellitus (GDM) mothers and hyperbilirubinemia, hypoglycemia, and hospitalization in their newborns. Henceforth, this study aims to study how these risks change on prenatal vitamin D supplementation.

Methods: Randomized parallel arm trials comparing these interventions' effect on the above outcomes were searched in the PubMed, Embase, and Scopus, irrespective date, and language of publication. Each eligible trial's risk of bias was assessed using the Cochrane collaboration tool. Using random-effects meta-analysis, the risk of the outcomes was compared.

Results: Six eligible Iran-based trials of about 476 participants were included in this review. Four trials complemented vitamin D along with other nutrients. Overall, the risk of bias was low in these trials. The newborns of antenatal vitamin D recipients have a reduced risk of hyperbilirubinemia (relative risk [RR] = 0.46; 95% confidence interval [CI]: 0.33, 0.64; $I^2 = 0\%$) and hospitalization (RR = 0.46; 95% CI: 0.32, 0.65; $I^2 = 0\%$) than those who did not receive the supplement. The rest of the outcomes did not vary between the compared interventions. The results remained unchanged on using a fixed-effect meta-analysis, repeating the meta-analysis while eliminating a trial each time, and on imputation analysis. An auxiliary meta-analysis comparing the intervention with placebo also suggested a decreased risk of hyperbilirubinemia (RR = 0.43; 95% CI: 0.30, 0.62; $I^2 = 0\%$) and hospitalization (RR = 0.44; 95% CI: 0.30, 0.62; $I^2 = 0\%$).

Conclusion: Newborns of GDM mothers who received vitamin D as a sole or co-supplement antenatally have a decreased risk of hyperbilirubinemia and hospitalization.

Keywords: Diabetes, gestational, hospitalization, hypoglycemia, jaundice, neonatal, Vitamin D

Introduction

Gestational diabetes mellitus (GDM) is the carbohydrate intolerance that develops during pregnancy.[1] During the 24–28 weeks of gestation, pregnant women with no previous diabetes history are screened for GDM.[2] GDM management begins with self-monitoring of blood glucose and lifestyle modification (e.g., dietary changes and physical activity).[3,4] When it fails to achieve glycemic control, pharmacotherapy with insulin is initiated.[3] A complicated GDM can affect both the mother and fetus adversely.[5] Jaundice and hypoglycemia are two important neonatal complications that occur in newborns of GDM mothers.[5]

Bilirubin deposition led yellowish discoloration of skin and sclera of newborn babies is referred to as neonatal jaundice.[6] It can be pathological and physiologic when it occurs during the first 24 h of life and between 2 and 4 days following birth, respectively.[7] Newborn hyperbilirubinemia is further classified as unconjugated and conjugated hyperbilirubinemia. Unconjugated hyperbilirubinemia may be pathologic or physiologic.[7] Whereas, conjugated hyperbilirubinemia, which occurs in hepatobiliary ailments like biliary atresia and choledochal cyst, is always pathologic.[7] Neonatal hyperbilirubinemia is a common complication of GDM pregnancies and is more common than pregnancies with no glucose intolerance.[8] The hyperinsulinemic environment inside the uterus of GDM mothers perhaps leads to hyperbilirubinemia in their newborns.[8] Although neonatal jaundice is a mild and transient phenomenon in most infants, its prevention is essential because bilirubin, if accumulated at very high-levels, can cross the blood-brain barrier and lead to bilirubin-induced

neurologic dysfunction and acute bilirubin encephalopathy.[7,9] Acute bilirubin encephalopathy might manifest with abnormal behavior, lethargy, opisthotonos, and seizures.[7,9] It may worsen further to develop kernicterus, a permanent neurologic sequela which is characterized by features like cerebral palsy, seizures, and sensorineural hearing loss.[7,9]

Next, hypoglycemia is another potential complication that occurs to the newborns of the GDM mothers. Due to the high blood glucose levels, the glucose from the GDM mother crosses the placenta and stimulates excessive fetal insulin production.[10,11] At birth, when the umbilical cord is clamped, the augmented insulin secretion in the fetus continues, which increases the risk of hypoglycemia in the newborn.[10,11] Moreover, the infants of diabetic mothers low catecholamine levels due to the relative adrenal insufficiency and their poor ability to mobilize the glycogen stores puts them at an additional risk of hypoglycemia.[12] Since blood glucose is essential for brain cell functioning,[10] preventing hypoglycemia, or reducing its duration is vital to avoid adverse neurological consequences.[11]

If newborns develop hyperbilirubinemia or hypoglycemia, treatment is given to prevent their complications. Phototherapy and exchange transfusion (gold standard) is used to prevent the complications of unconjugated hyperbilirubinemia.[6] On the other hand, hypoglycemia management depends on blood glucose levels and symptoms. For instance, intravenous glucose is infused in all symptomatic newborns with blood glucose levels <40 mg/dL, as per recommendations of the American Academy of Pediatrics.[13] Whereas, asymptomatic term formula-fed newborns who are at risk of hypoglycemia would require more frequent feeding and at a blood glucose level <25 mg/dL (from birth to first 4 h of life) or <35 mg/dL (four to 24 h of life) would need parenteral glucose.[14] Dextrose, diazoxide, glucagon, glucocorticoids, and dexamethasone are other therapeutic agents used to treat neonatal hypoglycemia.[11] While these are the therapeutic options for hyperbilirubinemia and hypoglycemia in neonates, little research has been done to prevent their occurrences in the newborns of GDM mothers.

In this regard, antenatal vitamin D supplementation's role in GDM is a novel research area since evidence points towards a possible link between vitamin D deficiency and GDM.[15-19] Contemporary clinical trials have explored the plausible role of antenatal vitamin D supplementation on neonatal outcomes.[20,21] However, best known to us, there is no systematic reviewing effort to synthesize the overall evidence on how antenatal vitamin D supplementation in GDM patients may help in determining the risk of the above outcomes in their neonates. Therefore, in this paper, we review this under-reviewed area of perinatal medicine.

The intervention

Vitamin D (calciferol) is a fat-soluble vitamin and is available in two inactive forms – D2 (ergocalciferol) and D3 (cholecalciferol).[22] Both forms are commercially available in dietary supplements and fortified foods.[22] After undergoing hydroxylation in the human body, they are converted into calcitriol, the biologically active form.[22] Vitamin D through its receptors in the uterus and placenta plays a role in the physiology of pregnancy.[23] Vitamin D has been used in clinical trials on GDM patients. There is some evidence that vitamin D supplementation in GDM patients during the antenatal period helps in achieving better glycemic control.[24,25] While some trials used it as a sole supplement,[26-28] others have used it with other supplements such as magnesium, calcium, or zinc.[29,30] Various clinical trials administered it in various dosages orally. Two trials advised participants to take vitamin D orally at 50,000 IU,[27,30] 2–3 weeks apart for 3–8 weeks; whereas, other trials recommended at a dose of 200–500 IU 2 times a day for 6–16 weeks.[26,29] One trial administered it in GDM patients as a 300,000 IU single dose intramuscular injection.[28]

This study aims to compare the risk of hyperbilirubinemia and hypoglycemia between the antenatal vitamin D supplemented and non-supplemented GDM patients' newborns. The additional objective of this study was to explore the incidence of preeclampsia and preterm delivery in these GDM mothers and hospitalization of their newborns.

Methods

Eligibility criteria

Participants

Pregnant females of any age, diagnosed with GDM in their concurrent pregnancy. The diagnosis and treatment of GDM were accepted as per the trialists.

Intervention

The intervention group should have received vitamin D supplementation as a sole supplement or in combination with another supplement/s in any dose, by any route (e.g., oral and parenteral), and for any duration during their current pregnancy, whereas the comparator group may receive any supplement/s except vitamin D or placebo or no intervention.

Study design

Thi study was a randomized parallel arm (any number of arms) trial of any duration.

Outcome

All trials should have reported the incidence of hyperbilirubinemia and (or) hypoglycemia (primary outcome) in the newborns of the above described GDM patients. Hyperbilirubinemia should have been diagnosed when the neonate required phototherapy, or the total serum bilirubin level was at or above 15 mg/dl, 18 mg/dl, or 20 mg/dl at 25–48 h, 49–72 h and more than 72 h after birth, respectively.[31] Since there is no consensus on the diagnostic criteria of hypoglycemia

in newborns,[13] it was accepted as per the trialists definition. Preterm birth, preeclampsia, and newborn hospitalization were the secondary outcomes; however, they did not make up the inclusion criteria. The secondary outcomes were accepted as per the trialists' definition irrespective of the reason for hospitalization.

Exclusion criteria

1. Diabetes, except GDM subtype (such as type 1 or type 2 diabetes) and 2. Study design other than randomized controlled trials like observational study design or cross-over trials were excluded from the study.

This review does not have a pre-published protocol. It adheres to PRISMA[32] reporting guideline.

Search strategy

Different electronic databases (PubMed, Scopus, and Embase) were searched for the prospective trials that matched the above-mentioned eligibility criteria, irrespective of their date or language of publication. In addition, the references of the trials included in this review were searched. Title and abstract of the trials were searched using the following search terms – "vitamin D" OR vitamin-D OR calciferol OR "vitamin D2" OR ergocalciferol OR "vitamin D3" OR cholecalciferol AND "gestational diabetes" OR GDM AND "randomized controlled trial" OR "clinical trial." The following filters were used to narrow down the search results (when available) – "Clinical Trial" and "controlled clinical trial" OR "randomized controlled trial." The last date of PubMed database search was 25-March-2020. SS[1] performed this database search.

Trial selection and data abstraction

We scanned through the title and abstract of the papers retrieved from the database search to select the eligible trials. Papers seeming to match this review's recruitment criteria or where a decision of inclusion or exclusion was not feasible by reading the excerpts of the publications only; a full-text reading followed. The data of the study design details, population characteristics, interventions compared, and outcomes of interest were retrieved from the respective trials. We selected eligible trials for this review and extracted data from these independently to each other and resolved any disagreement by discourse.

Risk of bias assessment

Next, utilizing the Cochrane collaboration tool, the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and miscellaneous bias was assessed for each trial. Based on the random sequence generation method, together with its allocation concealment from the trial participants, the selection bias of the trials was assessed. The performance and detection bias was assessed by the appropriateness of the blinding method used for study personnel and participants and outcome assessors, respectively. Attrition bias was assessed by the balance and reasons for participants with missing outcome data between different intervention arms. By contrasting the prespecified intentions to the results reported in the publication, the reporting bias of the trials was judged. The bias not fitting any of the above types were labeled as miscellaneous bias.

The risk of bias for each of these components was categorized as high risk, low risk, or unclear risk.[33]

A third-party opinion was not required to resolve disagreements between the authors. The trialists of the reviewed trials were not contacted.

Data synthesis and analysis

Next, for respective outcomes, using a random-effect model meta-analysis (DerSimonian and Laird method), the effect (in risk ratios) of the compared interventions was compared. Besides, the predictive intervals were calculated. For the meta-analysis, the number of newborns with a particular outcome was combined when they occurred in different treatment arms receiving the same type of intervention. For instance, if a trial had more than one treatment arm that received vitamin D containing supplements, the outcomes across such treatment groups were collated. When an outcome did not happen to either of the compared intervention groups, it was excluded from the meta-analysis. When the outcome occurred in any one of the contrasted treatment groups, 0.5 was added to each cell of the 2 × 2 table (continuity correction).

Statistical inconsistency assessment included I^2 statistics (0–40%, 30–60%, 50–90%, and 75–100% were categorized as less, moderate, substantial, and considerable heterogeneity, respectively) in conjunction with a *P*-value of Cochrane's Q (statistical significance determined at $P < 0.1$).[33] Visual inspection of funnel plots and contour-enhanced funnel plots was used to evaluate publication bias. Finally, for the individual outcomes, the sensitivity analyses were conducted by iterating the meta-analysis using a fixed-effect model (inverse variance method) and also by eliminating a trial each time.

Imputation case analysis (ICA)

Given the importance of missing outcome data in antenatal vitamin D supplemented GDM patients, we included an ICA for newborn hyperbilirubinemia to assess missing outcome data's impact on it.[34,35] For newborn hyperbilirubinemia, ICA was performed to assess missing outcome data's impact on it. As a part of ICA, we performed a complete cases analysis as our reference and compared its results with the following

assumptions: ICA-0 (missing participants not affected), ICA-1 (missing participants affected), ICA-b (worst case scenario, missing participants in treatment arm suffers the outcome), ICA-w (best case scenario, missing participants in control arm suffers the outcome), and Gamble and Hollis analysis[36] (using the results of ICA-b and ICA-w it inflates the uncertainty of the trials).[37] Since the outcomes in this study are adverse events, the ICA-b and ICA-w assumptions hold opposite to its traditional ones; that is, instead of the best-case, the ICA-b represented worst-case scenario, and instead of the worst-case, the ICA-w represented the best-case scenario.

Supplementary analysis

We included a supplementary meta-analysis to compare how the risk of each of the outcomes tested in this paper varies between vitamin D (as a sole or with other nutrients) and placebo recipients.

The statistical significance of the meta-analysis findings was estimated at a $P < 0.05$ and 95% confidence interval (CI). All analyses used Stata statistical software (StataCorp, College Station, Texas, USA).

Results

Selected articles

The database search produced 183 results. After excluding the duplicates, 112 titles and abstracts were scanned, and 17 papers required full-text reading. Finally, this systematic review and meta-analysis incorporated six trials [Figure 1],[20,21,38-41] conducted in Iran, on nearly 476 GDM patients.

Description of studies

These trials were single centered[20,21,38-42] (except that by Karamali, 2016),[20] published between 2015 and 2019. The mean age of the participants of the trials was between 28 and 32 years.[20,21,38-41] In two trials, vitamin D was the sole supplement received by the intervention group.[39,41] In the remaining trials,[20,21,38,40] besides vitamin D, the intervention arm participants received other supplements (e.g., probiotics, magnesium, calcium, and omega-3 fatty acids). While the comparator group of most trials received placebo and (or) non-vitamin D based supplements (omega-3 fatty acids), this group did not receive any intervention, in one trial.[39]

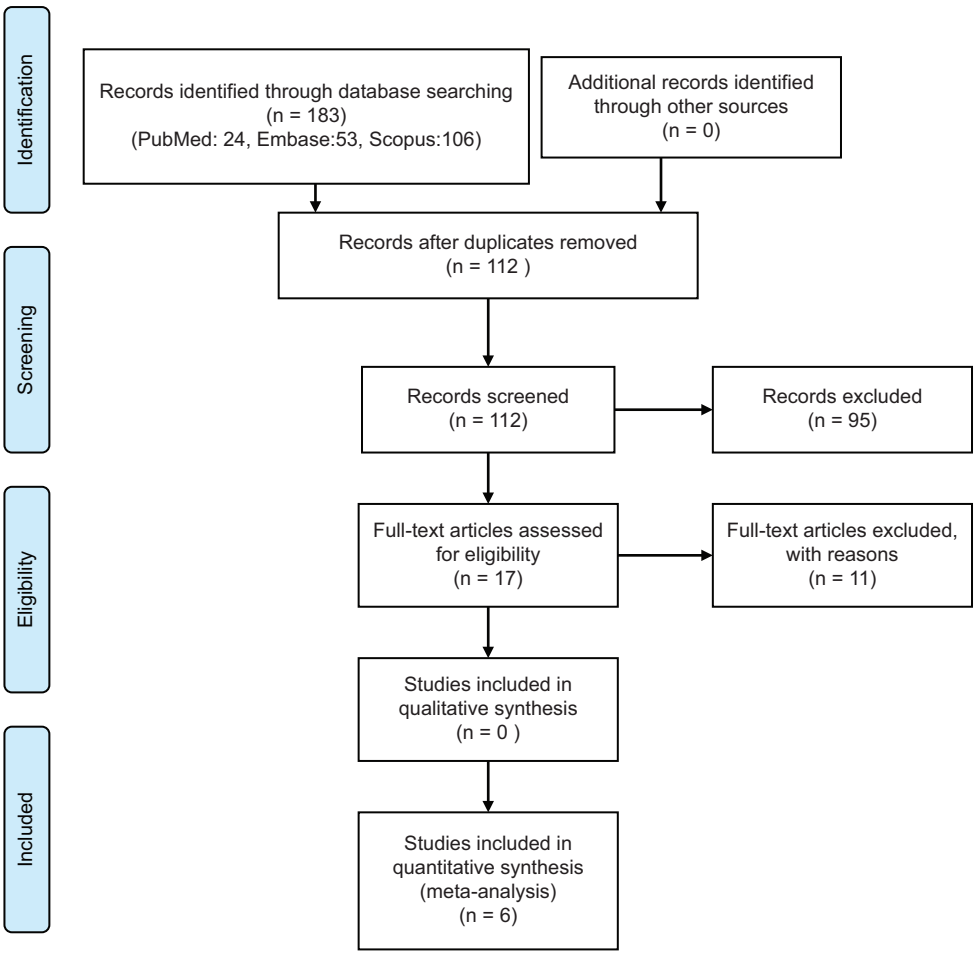

Figure 1: PRISMA 2009 flow diagram. (From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097)

Regarding the outcomes, all trials[20,21,38-41] reported newborn hyperbilirubinemia, preeclampsia, and preterm delivery. Two trials did not report the hypoglycemia[40] and hospitalization[39] of the newborns, respectively [Table 1]. Two different trials (Jamilian, 2019a,[21] Jamilian, 2019b)[40] had identical first author's last name and the year of publication; henceforth, a letter was suffixed to distinguish them in the tables and figures.

Risk of bias assessment

Overall, the trials are at low risk of bias [Table 2; Figures 2 and 3].[20,21,38-41] Across these trials, how the intervention allocation was concealed from the participants remains unclear.[20,21,38-41] Since hypoglycemia and hyperbilirubinemia of neonates are unlikely to be affected by the subjectivity of the researchers and the participants, their lack of blinding, as seen in the study by Valizadeh *et al*. (2016) would not have increased the risk of performance bias.[39]

Meta-analysis findings

The summary of outcome data is presented in along with the forest plots [Figures 4-8]. Meta-analysis using random-effect

Table 1: Salient features of reviewed papers

Study	Design	Participants	Interventions	Outcomes
Asemi, 2015[41]	Randomized, double-blind, placebo-controlled, single centered trial Funding information: Provided Ethical clearance: Obtained Trial ID: IRCT201305115623N7	Diagnosis: GDM Randomized (*n*)=50 Recruited 18–40-year-old's Mean age: 30.9 years Consent: Obtained Country: Iran	Two intervention arms: 1. Vitamin D: 50,000 IU vitamin D3 pearl 2 times during the trial period (at baseline and day 21) 2. Placebo: Twice (at baseline and day 21) Duration of intervention: 6 weeks.	1. Newborn hyperbilirubinemia 2. Newborn hypoglycemia 3. Newborn hospitalization 4. Preterm delivery 5. Preeclampsia
Jamilian, 2019a[21]	Randomized, double-blind, placebo-controlled, single centered trial Funding information: Provided Ethical clearance: Obtained Trial ID: IRCT201706075623N119	Diagnosis: GDM Randomized (*n*)=90 Recruited 18–40-year-old's Mean age: 30 years Consent: Obtained. Country: Iran	Three intervention arms: 1. Probiotic: 8×109 CFU/g 2. Vitamin D3 (50,000 IU) every 2 weeks plus 8×109 CFU/g probiotic 3. Placebo Duration of intervention: 6 weeks	1. Newborn hyperbilirubinemia 2. Newborn hypoglycemia 3. Newborn hospitalization 4. Preterm delivery 5. Preeclampsia
Jamilian, 2019b[40]	Randomized, double-blind, placebo-controlled, single centered trial Funding information: Provided Ethical clearance: Obtained Trial ID: IRCT201704225623N109	Diagnosis: GDM Randomized (*n*)=60 Recruited 18–40-year-old's Mean age: 28.4 years Consent: Obtained Country: Iran	Two intervention arms: 1. Vitamin D (200 IU) along with 100 mg magnesium, 4 mg zinc, 400 mg calcium twice daily 2. Placebo daily Duration of intervention: 6 weeks.	1. Newborn hyperbilirubinemia 2. Newborn hospitalization 3. Preterm delivery 4. Preeclampsia
Karamali, 2016[20]	Randomized, double-blind, Placebo-controlled, multicentric trial. Funding information: Provided Ethical clearance: Obtained Trial ID: IRCT201407115623N23	Diagnosis: GDM Randomized (*n*)=60 Recruited 18–40-year-old's Mean age: 30.15 years Consent: Obtained. Country: Iran	Two intervention arms: 1. Vitamin D3 (50,000 IU) at baseline and day 21 along with 1000 mg calcium carbonate daily 2. Placebo: Two placebos – one for vitamin D at baseline and day 21 and one for calcium every day Duration of intervention: 6 weeks	1. Newborn hyperbilirubinemia 2. Newborn hypoglycemia 3. Newborn hospitalization 4. Preterm delivery 5. Preeclampsia
Razavi, 2017[38]	Randomized, double-blind, placebo-controlled, single centered[42] trial Funding information: Provided Ethical clearance: Obtained Trial ID: IRCT201701305623N106	Diagnosis: GDM Randomized (*n*)=120 Recruited 18–40-year-old's Mean age: 29.67 years Consent: Obtained. Country: Iran	Four intervention arms: 1. Vitamin D (50000 IU) two weekly and placebo for omega-3 fatty acids 2 times a day 2. Vitamin D (50,000 IU) two weekly plus 1000 mg omega-3 fatty acids 2 times a day 3. 1000 mg omega-3 fatty acids 2 times a day and placebo for vitamin D two weekly 4. Placebo Duration of intervention: 6 weeks	1. Newborn hyperbilirubinemia 2. Newborn hypoglycemia 3. Newborn hospitalization 4. Preterm delivery 5. Preeclampsia
Valizadeh, 2016[39]	Randomized, single centered trial Investigators and patients were not blinded Funding information: Provided Ethical clearance: Obtained Trial ID: IRCT2012101611144N1	Diagnosis: GDM Randomized (n)=96 Mean age: 32.2 years Consent: Obtained. Country: Iran	Two arms: 1. 700,000 IU vitamin D3 in total (regimen differed by gestational age of GDM patients) 2. Comparison group did not receive any supplementation Duration of intervention: Until delivery	1. Newborn hyperbilirubinemia 2. Newborn hypoglycemia 3. Preterm delivery 4. Preeclampsia

Table 2: Risk of bias assessment[33]

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias) All outcomes	Blinding of outcome assessment (detection bias) All outcomes	Incomplete outcome data (attrition bias) All outcomes	Selective reporting (reporting bias)	Other bias
Asemi, 2015[41]	Low risk Comment: Computer generated random numbers were used	Unclear risk Comment: Precise mechanism how participants remained blinded of the allocation is not clear	Low risk Comment: Although the exact mechanism of blinding participants, personnel, and outcome assessor is not clear, it is unlikely that the outcome (hyperbilirubinemia) will be affected even if the blinding was broken		Low risk Comment: Outcome data were unavailable only for five participants	Low risk Comment: It reports the outcomes it intends to report	Low risk
Jamilian, 2019a[21]	Low risk Comment: Computer generated numbers were used	Unclear risk Comment: Precise mechanism how participants remained blinded of the allocation is not clear	Low risk Comment: Although the exact mechanism of blinding participants, personnel, and outcome assessor is not clear, it is unlikely that the outcome (hyperbilirubinemia) will be affected even if the blinding was broken		Low risk Comment: Outcome data were unavailable only for three participants	Low risk Comment: It reports the outcomes it intends to report	Low risk
Jamilian, 2019b[40]	Low risk Comment: Computer generated numbers were used	Unclear risk Comment: Precise mechanism how participants remained blinded of the allocation is not clear	Low risk Comment: Although the exact mechanism of blinding participants, personnel, and outcome assessor is not clear, it is unlikely that the outcome (hyperbilirubinemia) will be affected even if the blinding was broken		Low risk Comment: Outcome data available for all participants	Low risk Comment: It reports the outcomes it intends to report	Low risk
Karamali, 2016[20]	Low risk Comment: Computer generated numbers were used	Unclear risk Comment: Precise mechanism how participants remained blinded of the allocation is not clear	Low risk Comment: Although the exact mechanism of blinding participants, personnel, and outcome assessor is not clear, it is unlikely that the outcome (hyperbilirubinemia) will be affected even if the blinding was broken		Low risk Comment: Outcome data available for all participants	Low risk Comment: It reports the outcomes it intends to report	Low risk
Razavi, 2017[38]	Low risk Comment: Computer generated numbers were used	Unclear risk Comment: It is not clear if the numbered bottles were sequentially numbered and identical in appearance	Low risk Comment: Although the exact mechanism of blinding participants, personnel, and outcome assessor is not clear, it is unlikely that the outcome (hyperbilirubinemia) will be affected even if the blinding was broken		Low risk Comment: Outcome data available for all participants	Low risk Comment: It reports the outcomes it intends to report	Low risk
Valizadeh, 2016[39]	Low risk	Unclear risk	Low risk Comment: Although both investigators and participants were not blinded, it is unlikely that the outcomes of interest will be affected. For outcome assessment, hospital records were used.		Low risk	Low risk	Low risk

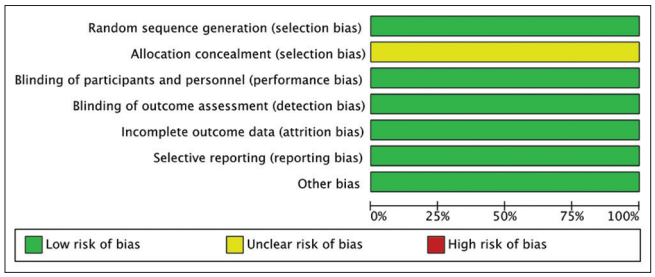

Figure 2: Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies

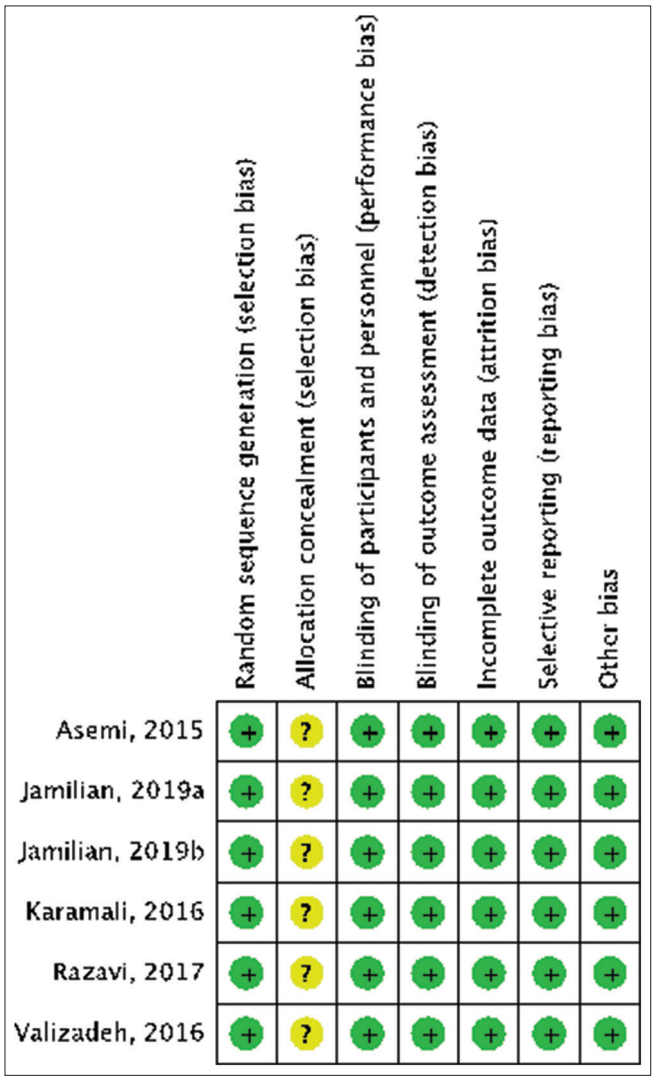

Figure 3: Risk of bias summary: Review authors' judgments about each risk of bias item for each included study

model shows that the supplementation of antenatal vitamin D (alone or as a co-supplement) in the GDM mothers decreased the risk of hyperbilirubinemia (relative risk [RR] = 0.46; 95% CI: 0.33, 0.64; $P < 0.001$; $I^2 = 0\%$; *P*-value of Cochrane's Q $P = 0.902$) and hospitalization (RR = 0.46; 95% CI: 0.32, 0.65; $P < 0.001$; $I^2 = 0\%$; *P*-value of Cochrane's Q $P = 0.821$) in their newborns compared no such supplementation [Figures 4 and 5]. The predictive intervals for jaundice (0.28–0.73) and hospitalization (0.26–0.81) in the neonates suggested that these findings are unlikely to be changed in a future trial. For the remaining outcomes, the incidence did not vary between the compared interventions [Figures 6-8]. The funnel plots and contour-enhanced funnel plots did not suggest any publication bias due to any small study effect [Figure 9]. The summary estimates and heterogeneity for all of the outcomes did not change on iterating the meta-analysis using a fixed-effect model [Figures 4-8] or on omitting one study each time [Table 3].

ICA

Three[21,39,41] of the six trials had missing outcome data. Across all six-imputation analyses, the prenatal vitamin D supplementation decreased the risk of hyperbilirubinemia in their neonates compared to the newborns of no vitamin D supplementation receiving GDM mothers, suggesting robustness to our preliminary meta-analysis [Figure 10].

Supplementary analysis

These analyses replicated the results of the primary analysis. The intervention decreased the risk of hyperbilirubinemia (RR = 0.43; 95% CI: 0.30, 0.62; $P < 0.001$; $I^2 = 0\%$; *P*-value of Cochrane's Q $P = 0.690$) and hospitalization (RR = 0.44; 95% CI: 0.30, 0.62; $P < 0.001$; $I^2 = 0\%$; *P*-value of Cochrane's Q $P = 0.732$). These results were identical in both the random-effect and fixed-effect model [Table 4].

Discussion

To summarize, six trials[20,21,38-41] published between 2015 and 2019 and based on about 476 GDM patients from Iran, were reviewed. Altogether, the trials have a low risk of bias.[20,21,38-41] Most trials used vitamin D as a co-supplement. Prenatal complementation of vitamin D with or without other supplements in GDM patients reduced the risk of jaundice and hospitalization in their newborns compared to neonates of GDM mothers receiving no intervention or no vitamin D containing supplement or placebo.

The evidence quality of the statistically significant meta-analytic findings was assessed by the GRADE approach (GRADE Working Group [2004]).[43] Since the trial participants originated from the population of one nation (Iran), the results may not be externally valid; therefore, we downgraded it by one level and graded the evidence as moderate-quality evidence.[20,21,32,38-41,43]

Next, we compare our results with other systematic reviews and meta-analysis. First, we contrast the neonatal outcomes. A systematic review and meta-analysis[44] comparing vitamin D supplementation with placebo in GDM patients did not find any difference between the compared

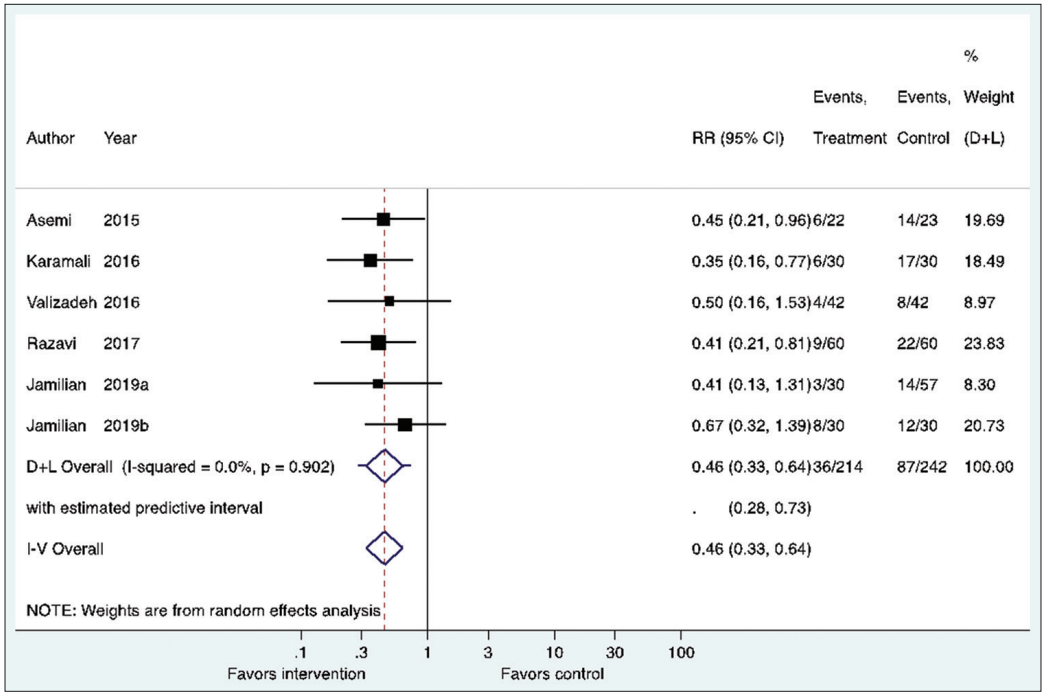

Figure 4: Outcome: Newborn hyperbilirubinemia. Forest plot showing findings of random effect (with estimated predictive interval) and fixed-effect model meta-analysis

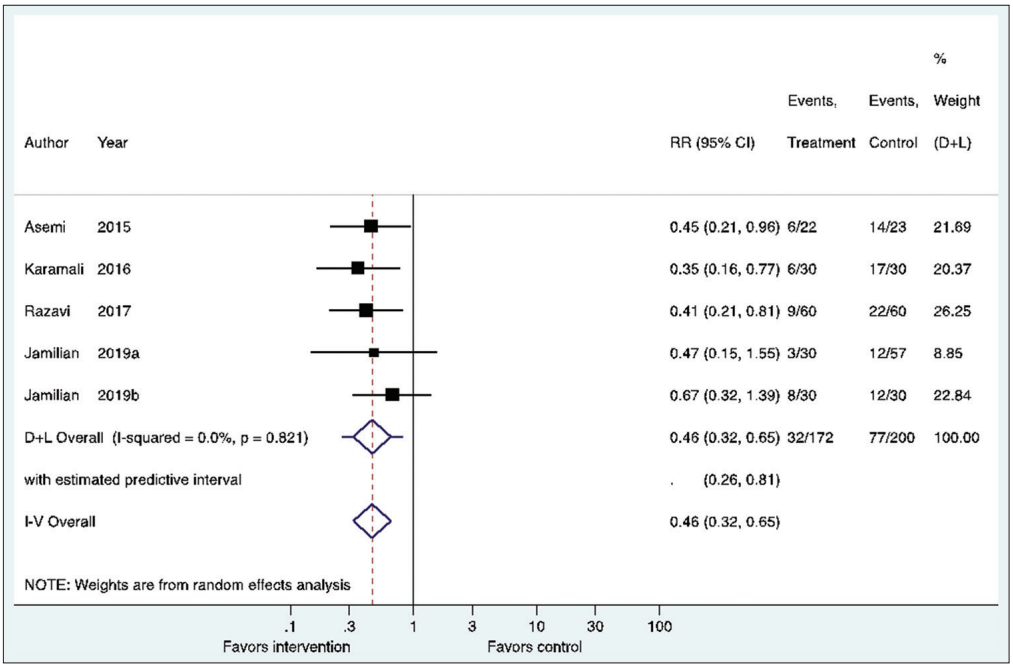

Figure 5: Outcome: Newborn hospitalization. Forest plot showing findings of random effect (with estimated predictive interval) and fixed-effect model meta-analysis

intervention groups for newborn hypoglycemia and found a decreased risk of hyperbilirubinemia in the vitamin D supplemented group. Although these results are identical to ours, it is important to note that the said meta-analysis[44] was based on two trials[27,41] only, of which we found one[41] to be legitimate. For the other trial,[27] the reporting in the meta-analysis (as depicted in its forest plot)[44] was perhaps not accurate since the trial[27] did not report these neonatal outcomes.

Then, both in the primary and the supplementary analysis, we found no difference in the incidence of preterm delivery

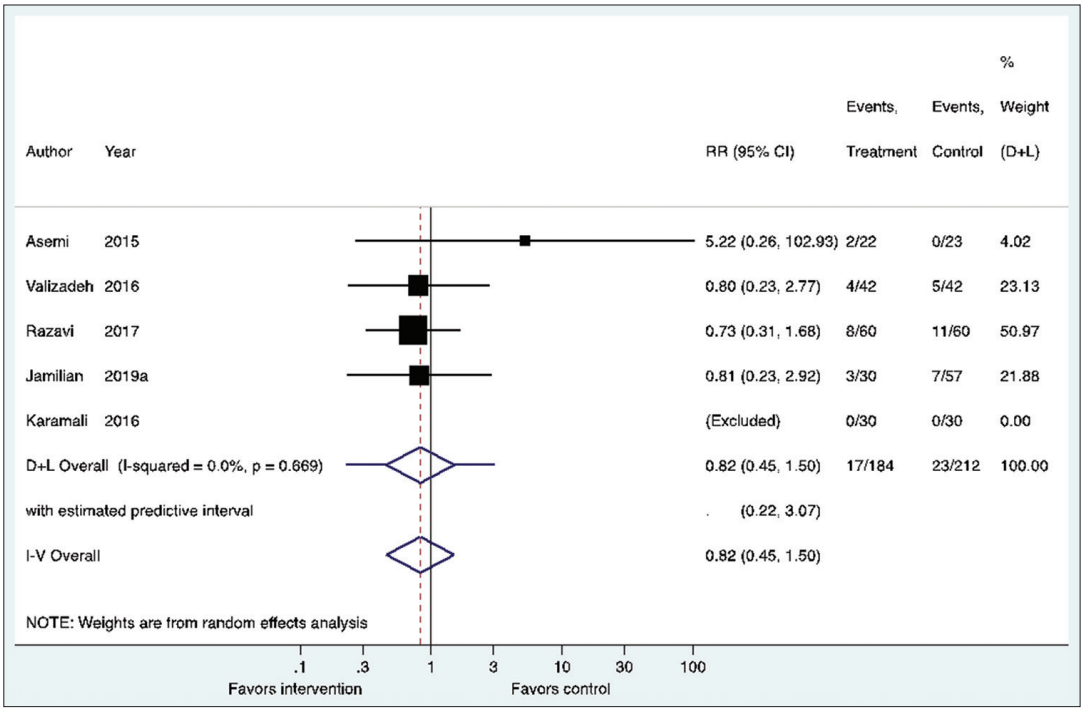

Figure 6: Outcome: Newborn hypoglycemia. Forest plot showing findings of random effect (with estimated predictive interval) and fixed-effect model meta-analysis

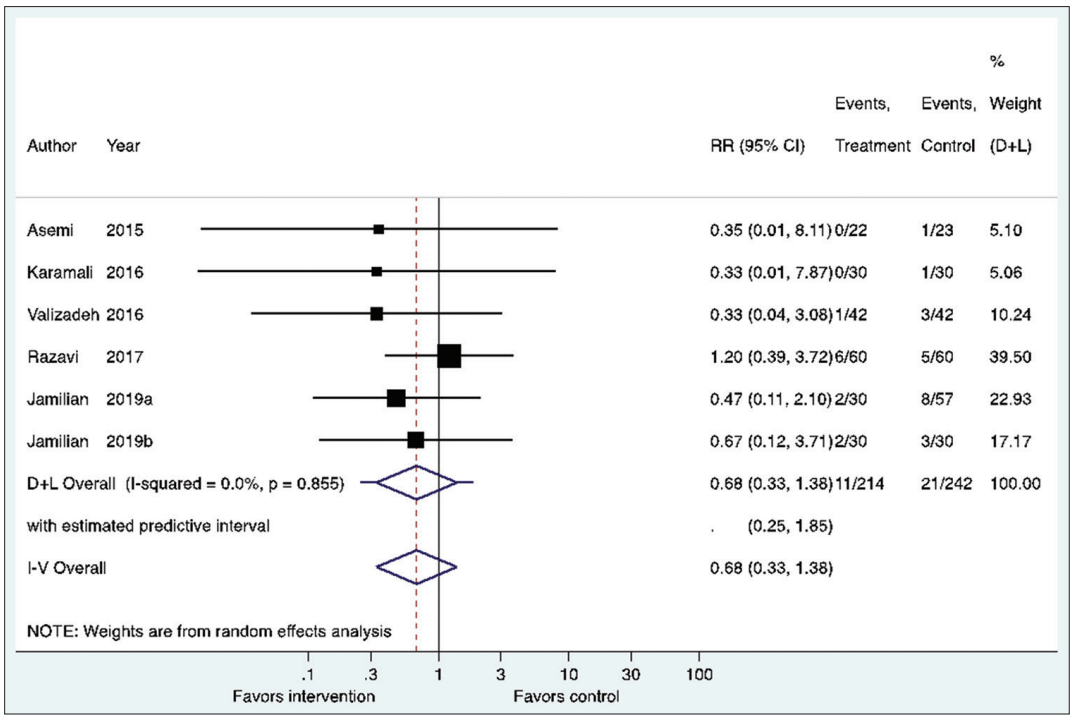

Figure 7: Outcome: Preeclampsia. Forest plot showing findings of random effect (with estimated predictive interval) and fixed-effect model meta-analysis

and preeclampsia, which resembled that of another systematic review and meta-analysis comparing the effect of antenatal vitamin D supplementation with placebo.[45] The study participants' recruitment criteria of the latter, however, varied from this study based on the participants' age (included 18 years or older pregnant females),[45] GDM diagnostic criteria (American Diabetes Association's criteria),[45-47] gestational age of GDM diagnosis (24–28 weeks of gestation),[45] and the GDM therapy received (recruited participants who did not require insulin therapy during their intervention period).[45]

Table 3: Sensitivity analysis (by dropping one trial for every meta-analysis) of outcomes in prenatal vitamin D supplemented versus non-supplemented gestational diabetes mellitus mothers and their neonates

Outcome	Dropped study		RR (95% CI)		*P*-value	Heterogeneity	
	Author	Year	RE model (RR, CI)	FE model (RR, CI)		I^2 statistics (%)	*P*-value of Cochrane's Q
Neonatal outcome							
Hyperbilirubinemia	Asemi[41]	2015	0.46 (0.32, 0.67)	0.46 (0.32, 0.67)	<0.001	0	0.811
	Jamilian[21]	2019a	0.46 (0.33, 0.66)	0.46 (0.33, 0.66)	<0.001	0	0.818
	Jamilian[40]	2019b	0.41 (0.28, 0.60)	0.41 (0.28, 0.60)	<0.001	0	0.989
	Karamali[20]	2016	0.48 (0.33, 0.70)	0.48 (0.33, 0.70)	<0.001	0	0.897
	Razavi[38]	2017	0.47 (0.32, 0.69)	0.47 (0.32, 0.69)	<0.001	0	0.833
	Valizadeh[39]	2016	0.45 (0.32, 0.64)	0.45 (0.32, 0.64)	<0.001	0	0.815
Hypoglycemia	Asemi[41]	2015	0.76 (0.42, 1.41)	0.76 (0.42, 1.41)	0.386	0	0.986
	Jamilian[21]	2019a	0.83 (0.42, 1.63)	0.83 (0.42, 1.63)	0.584	0	0.459
	Razavi[38]	2017	0.94 (0.40, 2.21)	0.94 (0.40, 2.21)	0.888	0	0.501
	Valizadeh[39]	2016	0.83 (0.42, 1.65)	0.83 (0.42, 1.65)	0.598	0	0.459
Hospitalization	Asemi[41]	2015	0.46 (0.31, 0.69)	0.46 (0.31, 0.69)	<0.001	0	0.676
	Jamilian[21]	2019a	0.46 (0.32, 0.66)	0.46 (0.32, 0.66)	<0.001	0	0.676
	Jamilian[40]	2019b	0.41 (0.28, 0.61)	0.41 (0.28, 0.61)	<0.001	0	0.969
	Karamali[20]	2016	0.49 (0.33, 0.73)	0.49 (0.33, 0.73)	<0.001	0	0.804
	Razavi[38]	2017	0.48 (0.32, 0.72)	0.48 (0.32, 0.72)	<0.001	0	0.708
Maternal outcome							
Preeclampsia	Asemi[41]	2015	0.70 (0.34, 1.46)	0.70 (0.34, 1.46)	0.341	0	0.777
	Jamilian[21]	2019a	0.75 (0.34, 1.69)	0.75 (0.34, 1.69)	0.491	0	0.795
	Jamilian[40]	2019b	0.68 (0.31, 1.48)	0.68 (0.31, 1.48)	0.332	0	0.744
	Karamali[20]	2016	0.70 (0.34, 1.46)	0.70 (0.34, 1.46)	0.344	0	0.781
	Razavi[38]	2017	0.47 (0.19, 1.16)	0.47 (0.19, 1.16)	0.101	0	0.988
	Valizadeh[39]	2016	0.73 (0.35, 1.56)	0.73 (0.35, 1.56)	0.419	0	0.823
Preterm delivery	Asemi[41]	2015	0.63 (0.24, 1.69)	0.63 (0.24, 1.69)	0.358	0	0.851
	Jamilian[21]	2019a	0.63 (0.23, 1.69)	0.63 (0.23, 1.69)	0.358	0	0.847
	Jamilian[40]	2019b	0.63 (0.24, 1.69)	0.63 (0.24, 1.69)	0.362	0	0.854
	Karamali[20]	2016	0.47 (0.17, 1.32)	0.47 (0.17, 1.32)	0.154	0	0.992
	Razavi[38]	2017	0.63 (0.24, 1.69)	0.63 (0.24, 1.69)	0.361	0	0.854
	Valizadeh[39]	2016	0.59 (0.16, 2.18)	0.59 (0.16, 2.18)	0.433	0	0.829

CI: Confidence interval, FE: Fixed-effect, RE: Random-effect, RR: Risk ratio

Next, it is worth discussing here if accepting the GDM treatment as per the trialists introduced any bias in our findings. In this regard, we reviewed the GDM management used in the respective trials. Interestingly, in all trials, except one (by Valizadeh *et al*. (2016)),[39] the trial participants had a relatively well-controlled GDM since they did not need insulin therapy throughout their pregnancies.[20,21,38,40,41] However, the inclusion of one trial requiring insulin to manage GDM plausibly did not affect the meta-analysis findings since the results did not change on sensitivity analyses that excluded the trial [Table 4].[39]

Likewise, it may be debated if the observed results of this study are due to supplementation of vitamin D or its co-supplements, as the majority of the trials (66%) used vitamin D with another nutrient.[20,21,38,40] We addressed it here, narratively. The co-supplement use in the reviewed trials was inconsistent. For instance, calcium was used in two trials,[20,40] and each of the remaining co-supplements, probiotics,[21] magnesium,[40] zinc,[40] and omega-3 fatty acids,[38] was used in one of these trials only. Whereas, vitamin D was the only supplement used by all trials consistently; henceforth, the vitamin D plausibly has a major role in the results of this study. Furthermore, the total dosage of vitamin D used in most of the reviewed trials was relatively the same, between 100,000 and 150,000 IU.[20,21,38,41]

Next, we state the implications and strengths of this study. Healthcare providers such as obstetricians, neonatologists, and pediatricians may find it useful to expand their existing

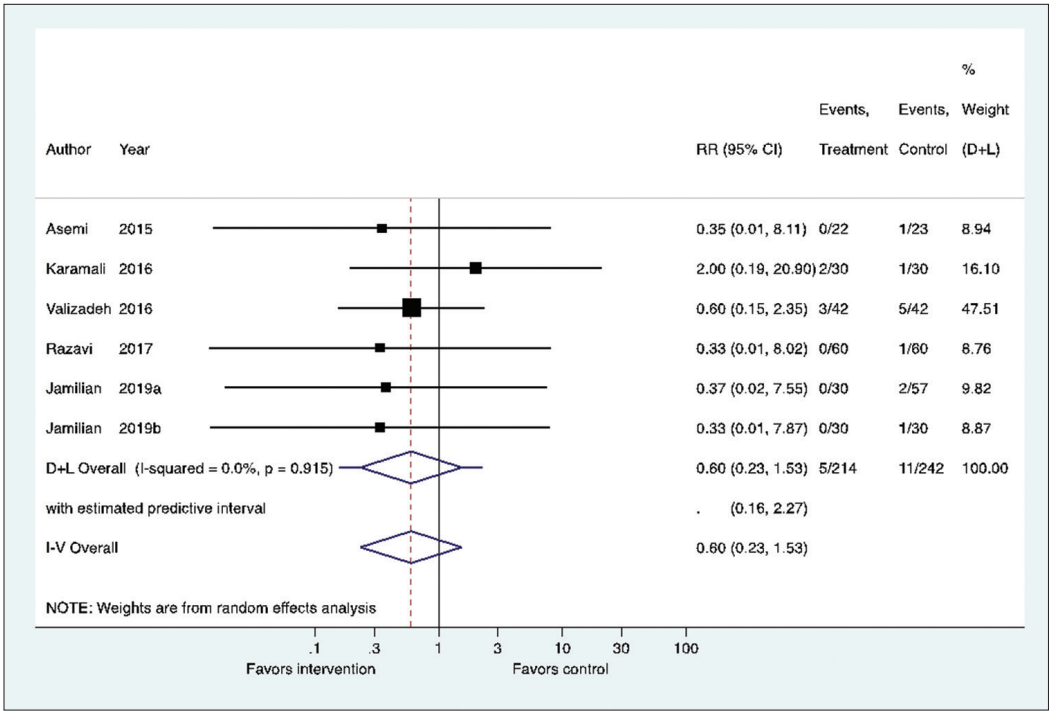

Figure 8: Outcome: Preterm delivery. Forest plot showing findings of random effect (with estimated predictive interval) and fixed-effect model meta-analysis

Table 4: Meta-analysis results: Prenatal vitamin D supplementation compared with placebo in gestational diabetes mellitus mothers and their neonates

Outcome	RR (95% CI)		*P*-value	Heterogeneity	
	RE model (RR, CI)	FE model (RR, CI)		I^2 statistics (%)	*P*-value of Cochrane's Q
Neonatal outcomes					
Hyperbilirubinemia	0.43 (0.30, 0.62)	0.43 (0.30, 0.62)	<0.001	0	0.690
Hypoglycemia	0.78 (0.36, 1.67)	0.78 (0.36, 1.67)	0.516	0	0.431
Hospitalization	0.44 (0.30, 0.62)	0.44 (0.30, 0.62)	<0.001	0	0.732
Maternal outcomes					
Preeclampsia	0.61 (0.27, 1.37)	0.61 (0.27, 1.37)	0.228	0	0.878
Preterm delivery	0.52 (0.14, 1.92)	0.52 (0.14, 1.92)	0.324	0	0.738

knowledge in the context. As all of the trials were Iran-based, from an Iranian perspective, it may aid in informing public health policy to decrease the burden of hyperbilirubinemia and hospitalization in neonates of GDM mothers. Besides, to test generalizability, our findings may encourage researchers across the globe to conduct trials similar to those reviewed here.

Regarding the strengths of this paper, this is perhaps one of the preliminary papers that systematically reviewed the context. An existing systematic review protocol aims to explore various maternal health effects of prenatal vitamin D supplementation; however, unlike this review, its objectives do not include the study of neonatal outcomes.[48] Then, our study's findings are likely to be strong as they are based on the highest level of epidemiological evidence, that is, randomized controlled studies. In addition, this review is likely to be more comprehensive as its database search was not limited to any language or date. Furthermore, the statistically significant chief meta-analytic findings are likely to be robust due to the absence of statistical heterogeneity, duplication of results on sensitivity analysis, and identical summary estimates in different imputation assumptions.

Despite these merits, this study has few limitations. Since some trials used vitamin D with co-supplements, we could not definitively distinguish if the latter might have played any role in this study's findings. Besides, the generalizability of our study remains uncertain, as all trials were conducted in Iran.

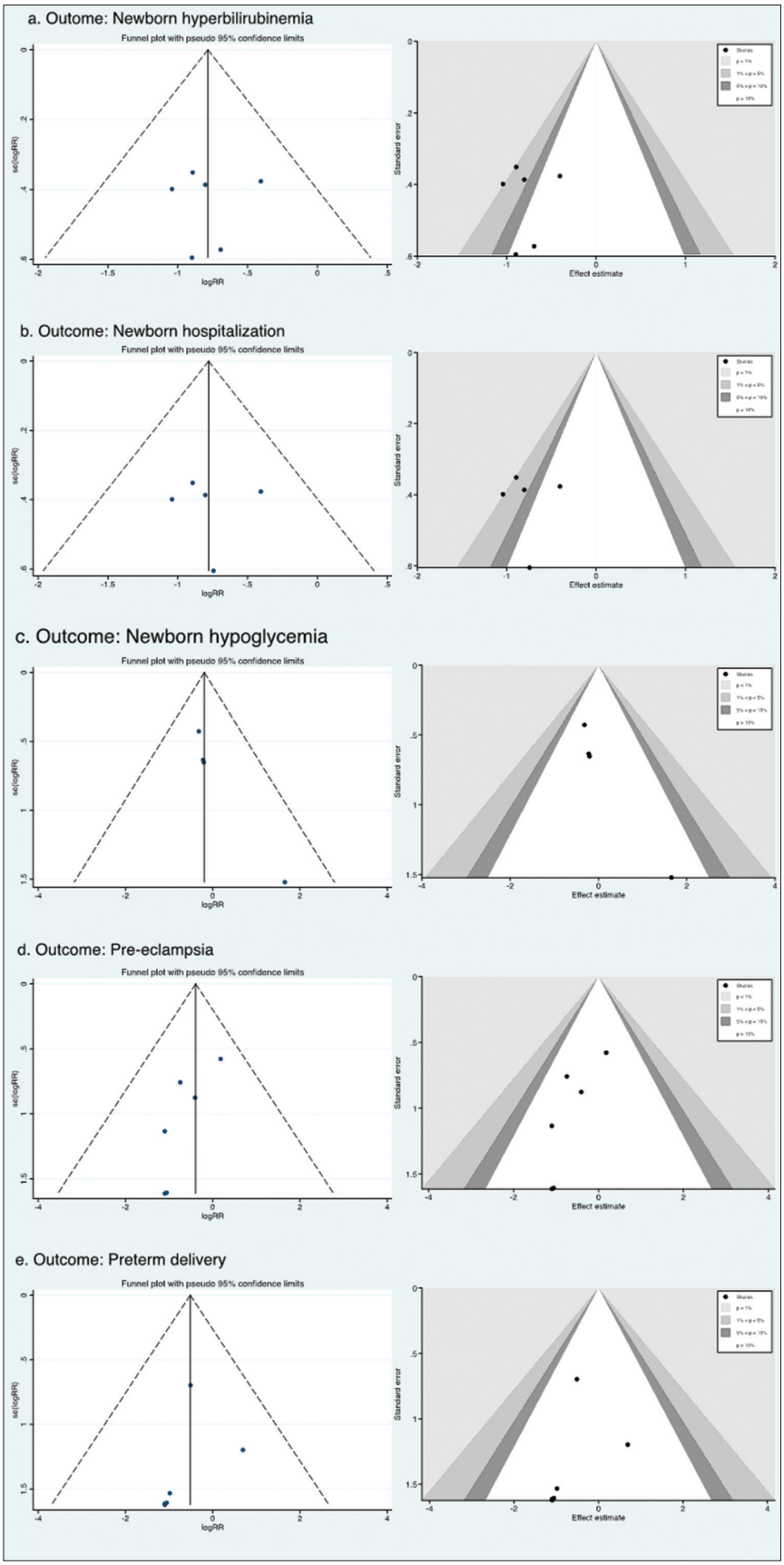

Figure 9: Funnel plots and contour-enhanced funnel plots evaluating publication bias for the meta-analytic comparison of perinatal outcomes between vitamin D supplemented and not supplemented gestational diabetes mellitus mothers

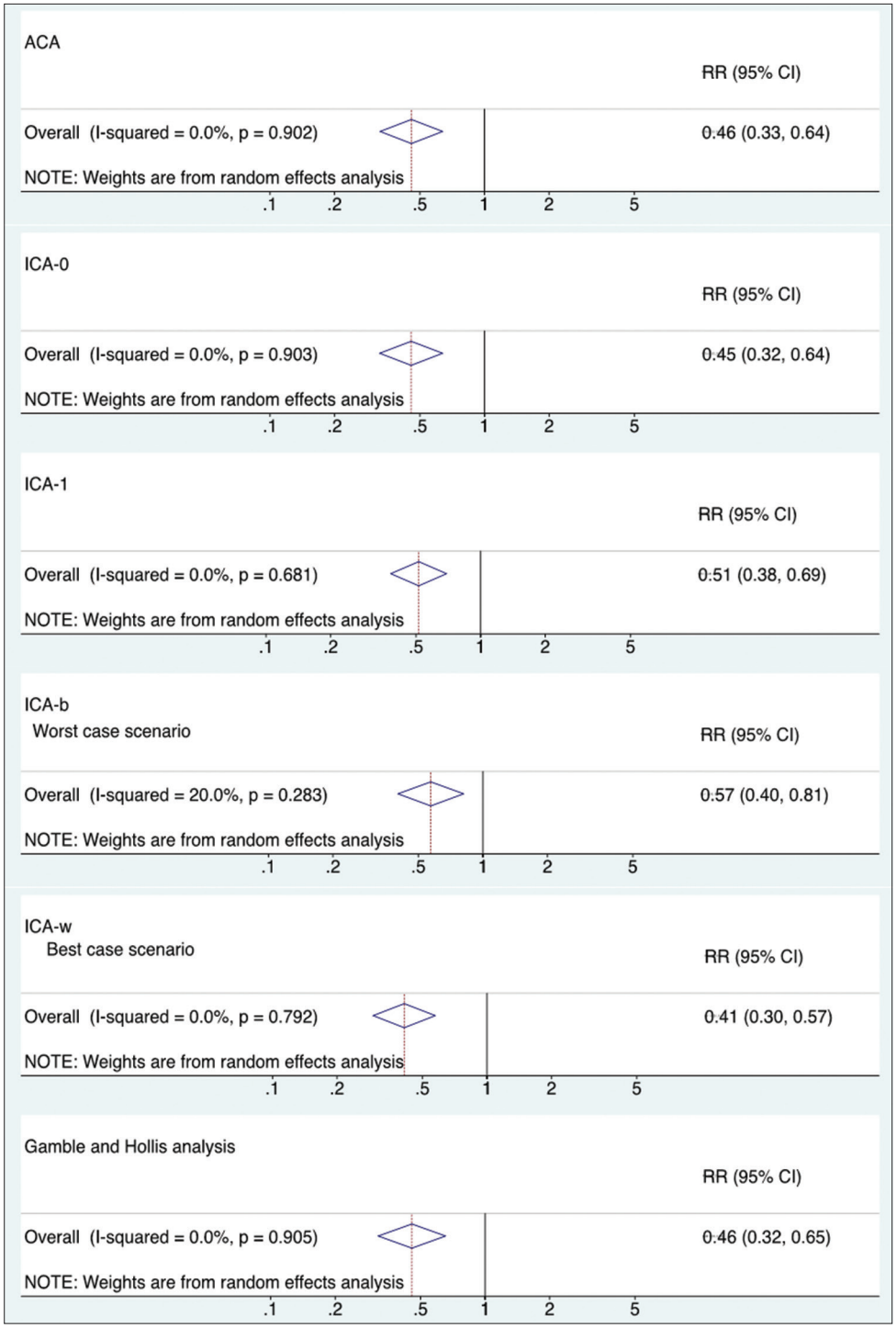

Figure 10: Outcome: Hyperbilirubinemia. Summary risk ratios estimated by different imputation case analysis assumptions. The left- and right-hand side of the treatment scale favors intervention and control, respectively. (ACA: Available case analyses; ICA-0: Imputation case analysis-no event; ICA-1: Imputation case analysis-event; ICA-b: Imputation case analysis-best case scenario; ICA-w: Imputation case analysis-worst case scenario)

Conclusion

Antenatal vitamin D supplementation in GDM patients, alone or as a co-supplement, decreases the risk of hyperbilirubinemia and hospitalization in their newborns compared to neonates of GDM patients who did not receive vitamin D as a supplement or received no intervention or received placebo only. Since all the trials were Iran-based, similar trials from other nations are required to evaluate the external validity of this research.

Authors' Declaration Statements

Ethics approval and consent to participate

Not applicable, as no human subjects were involved in this study.

Availability of Data and Material

Data related to this paper will be made available by the corresponding author upon receiving legitimate requests.

Competing Interests

On behalf of both the authors, the corresponding author states that there are no conflicts of interest.

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Authors' Contributions

SS[1] conceptualized and designed this study, performed database search, study selection, data abstraction, risk of bias assessment, analysis, and first and final draft of this manuscript. SS[2] contributed to the study selection, data abstraction, risk of bias assessment, and hard editing of the first draft.

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This work was done by the authors independently, and it is not related to their affiliated institutes. The affiliation of SS[1] was current at the time of submission of this manuscript to the journal. At present, SS[1] does not have an affiliation.

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References

1. Committee on Practice Bulletins-obstetrics. ACOG practice bulletin No. 190: Gestational diabetes mellitus. Obstet Gynecol 2018;131:e49-64.
2. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2019. Diabetes Care 2019;42:S13-28.
3. American Diabetes Association. 14. Management of diabetes in pregnancy: Standards of medical care in diabetes-2019. Diabetes Care 2019;42:S165-72.
4. Saha S. Compliance and barriers to self-monitoring of blood glucose in patients with gestational diabetes mellitus: A systematic review. Int J Health Sci (Qassim) 2019;13:44-52.
5. Rodriguez BS, Mahdy H. Gestational diabetes. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545196. [Last accessed on 2019 Dec 23].
6. Woodgate P, Jardine LA. Neonatal jaundice: Phototherapy. BMJ Clin Evid 2015;2015:0319.
7. Ansong-Assoku B, Ankola PA. Neonatal Jaundice. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2020. Available from: http://www.ncbi.nlm.nih.gov/books/NBK532930. [Last accessed on 2019 Dec 05].
8. Thevarajah A, Simmons D. Risk factors and outcomes for neonatal hypoglycaemia and neonatal hyperbilirubinaemia in pregnancies complicated by gestational diabetes mellitus: A single centre retrospective 3-year review. Diabet Med 2019;36:1109-17.
9. Wusthoff CJ, Loe IM. Impact of bilirubin-induced neurologic dysfunction on neurodevelopmental outcomes. Semin Fetal Neonatal Med 2015;20:52-7.
10. Begum S, Dey S, Fatema K. Neonatal glycemic status of infants of diabetic mothers in a tertiary care hospital. Indian J Endocrinol Metab 2018;22:621.
11. Sweet CB, Grayson S, Polak M. Management strategies for neonatal hypoglycemia. J Pediatr Pharmacol Ther 2013;18:199-208.
12. Abramowski A, Hamdan AH. Neonatal hypoglycemia. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2020. Available from: http://www.ncbi.nlm.nih.gov/books/NBK537105. [Last accessed on 2020 Jan 16].
13. Committee on Fetus and Newborn, Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics 2011;127:575-9.
14. Kalhan S, Peter-Wohl S. Hypoglycemia: What is it for the neonate? Am J Perinatol 2000;17:11-8.
15. Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: Systematic review and meta-analysis of observational studies. BMJ 2013;346:f1169.
16. Lu M, Xu Y, Lv L, Zhang M. Association between Vitamin D status and the risk of gestational diabetes mellitus: A meta-analysis. Arch Gynecol Obstet 2016;293:959-66.
17. Poel YH, Hummel P, Lips P, Stam F, van der Ploeg T, Simsek S. Vitamin D and gestational diabetes: A systematic review and meta-analysis. Eur J Intern Med 2012;23:465-9.
18. Wei SQ, Qi HP, Luo ZC, Fraser WD. Maternal Vitamin D status and adverse pregnancy outcomes: A systematic review and meta-analysis. J Matern Fetal Neonatal Med 2013;26:889-99.
19. Zhang MX, Pan GT, Guo JF, Li BY, Qin LQ, Zhang ZL. Vitamin D deficiency increases the risk of gestational diabetes mellitus: A meta-analysis of observational studies. Nutrients 2015;7:8366-75.
20. Karamali M, Asemi Z, Ahmadi-Dastjerdi M, Esmaillzadeh A. Calcium plus Vitamin D supplementation affects pregnancy outcomes in gestational diabetes: Randomized, double-blind, placebo-controlled trial. Public Health Nutr 2016;19:156-63.
21. Jamilian M, Amirani E, Asemi Z. The effects of Vitamin D and probiotic co-supplementation on glucose homeostasis, inflammation, oxidative stress and pregnancy outcomes in gestational diabetes: A randomized, double-blind, placebo-controlled trial. Clin Nutr 2019;38:2098-105.
22. Ross AC, Taylor CL, Yaktine AL, Del Valle HB. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: The National Academies Press; 2011.
23. Knabl J, Vattai A, Ye Y, Jueckstock J, Hutter S, Kainer F, *et al*. Role of placental VDR expression and function in common late pregnancy disorders. Int J Mol Sci 2017;18:2340.
24. Asemi Z, Hashemi T, Karamali M, Samimi M, Esmaillzadeh A. Effects of Vitamin D supplementation on glucose metabolism, lipid concentrations, inflammation, and oxidative stress in gestational diabetes: A double-blind randomized controlled clinical trial. Am J Clin Nutr 2013;98:1425-32.
25. Asemi Z, Samimi M, Tabassi Z, Shakeri H, Esmaillzadeh A. Vitamin D supplementation affects serum high-sensitivity C-reactive protein, insulin resistance, and biomarkers of oxidative stress in pregnant

women. J Nutr 2013;143:1432-8.

26. Li Q, Xing B. Vitamin D3-supplemented yogurt drink improves insulin resistance and lipid profiles in women with gestational diabetes mellitus: A randomized double blinded clinical trial. Ann Nutr Metab 2016;68:285-90.
27. Yazdchi R, Gargari BP, Asghari-Jafarabadi M, Sahhaf F. Effects of Vitamin D supplementation on metabolic indices and hs-CRP levels in gestational diabetes mellitus patients: A randomized, double-blinded, placebo-controlled clinical trial. Nutr Res Pract 2016;10:328.
28. Hosseinzadeh-Shamsi-Anar M, Mozaffari-Khosravi H, Salami MA, Hadinedoushan H, Mozayan MR. The efficacy and safety of a high dose of Vitamin D in mothers with gestational diabetes mellitus: A randomized controlled clinical trial. Iran J Med Sci 2012;37:159-65.
29. Karamali M, Bahramimoghadam S, Sharifzadeh F, Asemi Z. Magnesium-zinc-calcium-vitamin D co-supplementation improves glycemic control and markers of cardiometabolic risk in gestational diabetes: A randomized, double-blind, placebo-controlled trial. Appl Physiol Nutr Metab 2018;43:565-70.
30. Asemi Z, Karamali M, Esmaillzadeh A. Effects of calcium-vitamin D co-supplementation on glycaemic control, inflammation and oxidative stress in gestational diabetes: A randomised placebo-controlled trial. Diabetologia 2014;57:1798-806.
31. Porter ML, Dennis BL. Hyperbilirubinemia in the term newborn. Am Fam Physician 2002;65:599-606.
32. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. J Clin Epidemiol 2009;62:e1-34.
33. Higgins JP. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. United Kingdom: The Cochrane Collaboration; 2011. Available from: http://www.cochrane-handbook.org. [Last accessed on 2020 Aug 27].
34. Saha S. Impact of missingness on clinical trials on the effectiveness of antenatal Vitamin D supplementation in gestational diabetes mellitus patients. J Ideas Health 2020;3:138-9.
35. Saha S. A systematic review and meta-analysis protocol to compare the risk of attrition among prenatal Vitamin D supplemented gestational diabetes mellitus patients with its non-recipients. MedRxiv 2020;2020:0262.
36. Gamble C, Hollis S. Uncertainty method improved on best-worst case analysis in a binary meta-analysis. J Clin Epidemiol 2005;58:579-88.
37. Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. Clin Trials J Soc Clin Trials 2008;5:225-39.
38. Razavi M, Jamilian M, Samimi M, Ebrahimi FA, Taghizadeh M, Bekhradi R, *et al*. The effects of Vitamin D and omega-3 fatty acids co-supplementation on biomarkers of inflammation, oxidative stress and pregnancy outcomes in patients with gestational diabetes. Nutr Metab (Lond) 2017;14:80.
39. Valizadeh M, Piri Z, Mohammadian F, Kamali K, Moghadami HR. The Impact of Vitamin D supplementation on post-partum glucose tolerance and insulin resistance in gestational diabetes: A randomized controlled trial. Int J Endocrinol Metab 2016;14:e34312.
40. Jamilian M, Mirhosseini N, Eslahi M, Bahmani F, Shokrpour M, Chamani M, *et al*. The effects of magnesium-zinc-calcium-vitamin D co-supplementation on biomarkers of inflammation, oxidative stress and pregnancy outcomes in gestational diabetes. BMC Pregnancy Childbirth 2019;19:107.
41. Asemi Z, Karamali M, Esmaillzadeh A. Favorable effects of Vitamin D supplementation on pregnancy outcomes in gestational diabetes: A double blind randomized controlled clinical trial. Horm Metab Res 2015;47:565-70.
42. Asemi Z. Clinical Trial of the Effect of Combined Omega-3 Fatty Acids and Vitamin D Supplementation Compared with the Placebo on Metabolic Profiles and Pregnancy Outcomes in Patients with Gestational Diabetes. United Kingdom: Iranian Registry of Clinical Trials. 2017. Available from: http://www.en.irct.ir/trial/6136. [Last accessed on 2019 Oct 18].
43. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, *et al*. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
44. Jahanjoo F, Farshbaf-Khalili A, Shakouri SK, Dolatkhah N. Maternal and neonatal metabolic outcomes of Vitamin D supplementation in gestational diabetes mellitus: A systematic review and meta-analysis. Ann Nutr Metab 2018;73:145-59.
45. Saha S, Saha S. A comparison of the risk of cesarean section in gestational diabetes mellitus patients supplemented antenatally with Vitamin D containing supplements versus placebo: A systematic review and meta-analysis of double-blinded randomized controlled trials Saha. J Turk German Gynecol Assoc 2020;21:201-12.
46. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37:S81-90.
47. Rossi G, American Diabetes Association. Diagnosis and classification of diabetes mellitus. Recenti Prog Med 2010;101:274-6.
48. Saha S, Saha S. A comparison of the changes in gestational weight, body mass index, and serum Vitamin D level in gestational diabetes mellitus patients complemented with Vitamin D in contrast to those who did not receive the supplement: A protocol for systematic review and meta-analysis of randomised controlled trials. Int J Diabetes Metab 2019:1-6.