Review

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 and Saha. C-section and Vitamin D in GDM patients

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Abstract

This study aims to study the role of vitamin D containing supplements in the risk of cesarean section (CS), a common complication in gestational diabetes mellitus (GDM) patients. The additional objective was to assess the risk of developing pre-eclampsia, preterm delivery, macrosomia, and polyhydramnios in these participants.

Various electronic databases were searched for double-blinded parallel-arm randomized controlled trials that reported the incidence of CS in adult non-insulin treated GDM patients who received vitamin D and placebo in different treatment arms, respectively. Next, each eligible trial's risk of bias was assessed, and the effects of the above interventions on the respective outcomes were compared meta-analytically across the trials.

This review included five Iranian trials sourcing data from nearly 380 participants. The risk of bias in the trials was primarily low. In contrast to the placebo group, the risk of CS (RR=0.61, p=0.002, 95% CI=0.44,0.83; I^2=0%, p-value of Cochranes Q=0.373) and macrosomia (RR=0.31, p=0.006, 95% CI=0.13,0.72; I^2=0%, p-value of Cochranes Q=0.935) was lesser in the vitamin D supplemented group. The remaining outcomes did not differ between the intervention groups.

The antenatal use of vitamin D containing supplements in non-insulin treated GDM patients might reduce the risk of CS and macrosomia.

Keywords: Diabetes, Gestational; Vitamin D; Cesarean Section; Fetal Macrosomia; Pre-Eclampsia; Premature Birth; Polyhydramnios

Introduction

Gestational diabetes mellitus (GDM) is a glucose intolerance to any degree occurring at the start of pregnancy or first recognized during gestation.(1) It is diagnosed between 24-28 weeks of gestation using screening tests with a 50 gm and 1-hour glucose challenge test.(1) It is classified as A1GDM and A2GDM, depending on whether it is managed with dietary therapy or medication, respectively.(1) The chief medication used to treat GDM on the failure of diet and exercise therapy is insulin.(1) Glyburide and metformin, two oral hypoglycemic agents with the potential to cross the placenta, are also used to treat GDM frequently; however, such use of these medications is not approved by the U.S. Food and Drug Administration due to inadequate safety information.(1,2) Unlike type 1 and type 2 diabetes, newer drugs like sodium-glucose linked transporter 2 inhibitors, remains poorly studied in GDM patients.(3–5)

GDM can cause both neonatal (e.g., macrosomia, neonatal hypoglycemia, shoulder dystocia, hyperbilirubinemia) and maternal complications.(1,6) One of the chief maternal complications of GDM is the cesarean section (CS), in which the fetus is delivered surgically by incising the abdomen and uterus of the parturient.(1,7–9) The prevalence of CS is high in GDM patients (32-44%), and it is more common than parturient with no glucose intolerance.(7,10–15) Its indication is determined by the obstetric need of the GDM mother like pre-eclampsia, macrosomia, excessive fetal growth (e.g., fetal weight more than 4500 gm), and past obstetric history (e.g., previous history of childbirth by CS).(7,8,16–18) CS increases the risk of wound hematoma, anesthetic complications, major puerperal infection, and severe hemorrhage (needing hysterectomy).(19) Moreover, women undergoing planned vaginal delivery are less likely to have severe morbidity or mortality compared to those delivered by CS on an emergency basis.(19)

To minimize these surgical risks, it's vital to search for new pragmatic treatment options that can decrease the incidence of CS in GDM patients. In this regard, the plausible clinical role of antenatal vitamin D supplementation in GDM patients is a novel area to explore, as suggested by recent vitamin D-related research. Existing studies suggest a possible association between vitamin D deficiency and GDM.(20–24) Moreover, the GDM prevalence tends to decrease on prenatal supplementation of vitamin D.(25,26) Besides, the optimum vitamin D status during pregnancy might be protective against CS; although, the mechanism remains unclear.(27–29) When vitamin D is complemented in GDM patients, it helps in accomplishing better glycemic control. (e.g., decrease in fasting plasma glucose, insulin, and homeostasis model of assessment-insulin resistance).(20–24,30,31) All such vitamin D related findings in pregnancy and GDM rationalizes this paper's objective to explore the risk of CS in (antenatal) vitamin D supplemented GDM patients.

The intervention

Vitamin D is a fat-soluble hormone.(32) It is available from diet and supplements in two physiologically inactive forms - D2 (ergocalciferol) and D3 (cholecalciferol).(33,34) Vitamin D3 is additionally synthesized in the skin on exposure to the sun.(33) The active form of vitamin D, calcitriol (1,25(OH)2 D), is produced on hydroxylation of vitamin D2 and D3 successively in the liver and kidneys.(33,35) This active form plays a role in the physiology of pregnancy via the vitamin D receptors in the uteroplacental tissue.(33,35)

Recently, different clinical trials have tested the health effects of antenatal vitamin D supplementation in GDM patients. However, vitamin D's route of administration (parenteral(36) versus oral(37–40)), dosing, and the accompanying supplements (when used) varied among such trials. Some trials have used vitamin D as a sole supplement,(36–38) while others used it with co-supplements like magnesium, zinc, or calcium.(39,40) A trial that tested the role of intramuscularly administered vitamin D in GDM patients, used it as a single injection of 300 000 IU.(36) Whereas, clinical trials that prescribed it orally, advised GDM

patients to take it at a dose of 50000 IU, 2-3 weeks apart for 3-8 weeks.(38,40) Other such trials asked GDM patients to take 200-500 IU of oral vitamin D twice daily for 6-16 weeks.(37,41)

What this review adds?

In GDM patients, the contemporary evidence of antenatal vitamin D supplementation's effect on CS, and other obstetric outcomes are based on the clinical trials chiefly (like those reviewed in this paper). However, best known to us, there is no previous attempt to synthesize the overall rigor of such evidence by systematic review and meta-analysis. Therefore, this paper reviews this under-reviewed area of GDM literature and synthesizes new evidence based on the existing highest quality of epidemiolocal studies (i.e., double-blinded randomized clinical trials). Besides, as this study is on the GDM mothers who were not on insulin treatment, the latter's therapeutic effects are unlikely to bias this study's findings.

Aim

This study aims to compare the risk of CS between non-insulin treated GDM patients supplemented antenatally with vitamin D containing supplements and placebo. The auxiliary objective is to compare the risk of macrosomia, polyhydramnios, pre-eclampsia, and pre-term delivery among these treatment groups.

Materials and Methods

Inclusion criteria: 1. Study design: parallel-arm (any number of arms) double-blinded randomized controlled clinical trials of any duration were eligible. 2. Participant: The eligible participants were adult (18 years or older) females diagnosed with GDM (by American Diabetes Association's criteria(42,43)) between 24-28 weeks of their concurrent pregnancy who received the intervention of interest before initiation of insulin therapy. 3. Intervention compared: The above-described trials should compare the following interventions - vitamin D (in D2 or D3 form or both; as a sole supplement or adjunct to any other supplements) with placebo. Vitamin D supplementation was accepted irrespective of its dose and route of administration (oral or intramuscular). 4. Outcome: The trials must report the frequency of the CS observed in each of the afore-mentioned treatment groups post-intervention.

Exclusion criteria: 1. Study design besides the above (like observational study designs, single-arm interventional studies, and cross-over trials) were not included in this review. 2. Participants with diabetes of any other type except GDM (e.g., type 1 diabetes) or those diagnosed previously with GDM were excluded from this review.

The secondary outcomes of interest were macrosomia, polyhydramnios, pre-eclampsia, and pre-term delivery; however, they did not contribute to the inclusion criteria. This review follows the PRISMA(44) reporting guideline and does not have a pre-published protocol.

The search for eligible trials' titles and abstracts took place in electronic databases (PubMed, Embase, and Scopus) with no restriction to date or language. Following search strategy was used in PubMed: "vitamin D" OR calciferol OR "vitamin D2" OR ergocalciferol OR "vitamin D3" OR cholecalciferol OR cholecalciferol (MeSH) OR "ergocalciferols" (MeSH) AND "diabetes, gestational" (MeSH) AND "gestational diabetes" OR GDM. The search was restricted to clinical trials by using the filters "Clinical Trial" and "Randomized Controlled Trial." Identical search terms were used for searching the other databases. The last date of database search was 07-Feb-2020.

The papers extracted by the electronic database search were skimmed for trials matching this review's eligibility criteria. Publications were read in full text when they seemed to match these criteria or in circumstances where a decision of their inclusion or exclusion was not

possible by reading the titles and abstracts only. Besides the above, an auxiliary search was conducted in the references of the papers that were included in this review.
Then, following data were extracted from the recruited trials: author information (first author's last name and year of publication), study design (randomization, blinding, if placebo-controlled, single or multicentric, funding, ethical clearance, trial ID), participants (diagnosis, gestational age of GDM diagnosis, number randomized, mean age, participant consent, trial nation), interventions (interventions received by each of the trial arm), and outcomes. Using the Cochrane Collaboration's tool, these trials' risk of selection bias (based on random sequence generation and concealment of participant allocation), performance bias, detection bias, attrition bias, reporting bias and miscellaneous bias were assessed and categorized as high risk, low risk, and unclear risk.(45)
The first author conducted the database search and retrieved the eligible trials and their data. The co-author subsequently rechecked it. The risk of bias in the respective trials was assessed by the authors independently, and then the findings were matched. The authors resolved disputes in their opinion at all stages of this review by discussion.
The intervention effects on the outcomes were compared across the trials by the random-effect model meta-analysis (DerSimonian and Laird method), and the summary effect was determined in risk ratios (RR). Despite the relative homogeneity of the participant characteristics and study design, a random-effect model was used since the vitamin D supplement adjuncts used between the trails were not identical. To determine the effects of vitamin D as a chief supplement, in trials that used it in multiple treatment arms, we chose one that included a fewer number of vitamin D adjuncts. For meta-analyses, when an outcome occurred in one of the intervention arms of a trial only, 0.5 was added to each cell of the 2x2 table. Heterogeneity was assessed using the p-value of Cochranes Q (statistical significance determined at $p<0.1$) in conjunction with I_2 statistics (0-40%, 30-60%, 50-90%, and 75-100% represented less, moderate, substantial, and considerable heterogeneity respectively).(45) Funnel plots were used to assess (visually) publication bias.
Finally, sensitivity analyses followed, in which, the meta-analysis for the respective outcomes was iterated using a fixed-effect model (inverse-variance method) and also by excluding a study each time (using both fixed-effect and random effect model). At $p<0.05$, results were considered statistically significant. The Stata statistical software (StataCorp, College Station, Texas, USA) was used to perform statistical analyses.

Results

The electronic search returned 836 search results. After excluding the duplicates, the title and abstract of 757 papers were read. For 16 studies, full-text reading ensued. Finally, five trials meeting the eligibility criteria of this review were included for the risk of bias assessment and quantitative analysis (Figure 1).(46–50) These trials were published between 2015-19, primarily single centered(47–51) (except one)(46), and based on about 380 GDM patients from Iran. The average age of these participants was approximately between 28-32 years.(46–50)
Two of the trials(48,50) tested vitamin D as a sole supplement in one of their treatment arms.(48) In the remaining trials' intervention arm, vitamin D was co-supplemented with another supplement (e.g., probiotics, magnesium, calcium, and zinc).(46,47,49) All trials had a placebo arm.(46–50) Each trial reported, both the primary and secondary outcomes.(46–50)
Regarding the appraisal of the studies, overall the trials are at a low risk of bias except for unclear risk of allocation concealment in four trials(46,47,49,50) and performance bias in one trial.(47) Table 1 presents the salient features and the risk of bias assessment of the reviewed trials.(46–50)

Upon meta-analysis, GDM patients receiving vitamin D containing supplements had a lower risk of experiencing CS (RR=0.61, p=0.002, 95% CI=0.44,0.83; I_2=0%, p-value of Cochranes Q=0.373) and macrosomia (RR=0.31, p=0.006, 95% CI=0.13,0.72; I_2=0%, p-value of Cochranes Q=0.935) than the placebo recipients. The remaining outcomes' risk did not vary between the compared interventions. Overall, for all outcomes, statistical heterogeneity was less (i.e., between 0-40%).(45) The forest plots (Figure 2-6) depict the outcome data along with their effect sizes.
On visual inspection, the funnel plots (plots not shown) were not suggestive of any publication bias. Sensitivity analysis results are almost identical to the preliminary analyses (Table 2).

Discussion
To summarize, five recent double-blinded randomized controlled Iranian trials (comprising of about 380 GDM patients) compared the obstetric risk of CS, macrosomia, polyhydramnios, pre-eclampsia, and pre-term delivery between the prenatal recipients of vitamin D and placebo. The trials' risk of bias was predominantly low with occasional unclear risk of bias components.(46–50) The meta-analysis suggested that in GDM patients, the antenatal vitamin D containing supplement recipients have a reduced risk of CS and macrosomia than those who took a placebo.
The evidence quality of CS and macrosomia was graded using the GRADE approach (GRADE Working Group (2004)).(52) Due to the unclear risk of bias present in some of the trials, the evidence was downgraded by one level to moderate-quality evidence.
The scope of contrasting this review's findings with the existing literature is limited due to its conceptual novelty. In this regard, we could find a recent review by Cochrane collaboration comparing obstetric outcomes between the vitamin D (as a sole or complementary supplement) and placebo receiving pregnant females.(27) It found no major difference in the risk of CS between these intervention groups.(27) However, unlike this review it(27) was not specific to the GDM subpopulation.
Thereafter, the implications of this review are discussed here. First, healthcare professionals caring for GDM patients might find this review worthful to expand their existing knowledge in this context. Next, research in this milieu may help to inform public health policy about endorsing prenatal vitamin supplementation in GDM patients. The lower rates of macrosomia and CS due to vitamin D supplementation may encourage future researchers to investigate if the former led to the latter and its plausible pathophysiology. Moreover, future trialists from nations other than Iran may also consider researching the context to test if these paper's findings are externally valid or not.
The following are the strengths of this review. First, this is perhaps the first systematic review that attempted to synthesize evidence in this study's context. Second, the findings of this review are likely to be rigorous as it utilized evidence from double blinded randomized controlled trials, the highest level of epidemiological evidence. Third, this review is expected to be more comprehensive as its database search method was not restricted to any date or language. Lastly, the meta-analysis findings regarding the CS and macrosomia are likely to be robust due to their similarity with the sensitivity analysis.
Despite these strengths, there are certain limitations of this paper. At the review level, the number of trials investigating the context was relatively few, which might have compromised the external validity of our study. At outcome level, including intervention arms of trials that tested vitamin D along with other nutritional adjuncts, makes it difficult to conclude if the observed effects were influenced by the latter. At the study level, the weaknesses were the unclear risk of bias,(46,47,49,50) single centric study design,(47–50) and relatively small

sample size.(46–50) Additionally, as all trials were Iran-based,(46–50) the findings are unlikely to be generalizable to the global population.

Conclusion

The contemporary evidence in non-insulin treated GDM patients (in Iran) suggest that antenatal vitamin D containing supplements decreases the risk of cesarean section and macrosomia, compared to placebo. However, to increase the external validity of these findings, methodologically rigorous trials from different parts of the globe might be useful in future. Furthermore, future trials may use vitamin D as the sole supplement to specifically identify its effects on obstetric outcomes in GDM patients.

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Conflict of interest

None declared. The study was conducted by the authors independently and is not related to their affiliated institutions.

Statement of ethics

No human subjects were involved in this study; henceforth, an ethical approval was not needed.

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Table1. Salient features of reviewed papers and risk of bias assessment						
Study: Asemi, 2015 (50)						
Design		**Participants**	**Interventions compared**		**Reported outcomes**	
Randomized Double-blind Placebo-controlled Single centered Funding information: provided Ethical clearance: obtained Trial ID: IRCT201305115623N7		Diagnosis: GDM Gestational age of GDM diagnosis: 24-28 week Recruited 18-40-year old's Randomized (n) = 50 Mean age: 30.9 years Consent: obtained. Country: Iran	Two interventions: 1. Vitamin D: 50,000 IU vitamin D3 pearl twice during the trial period (at baseline and day 21) 2. Placebo: twice (at baseline and day 21) Duration of intervention: 6 weeks.		1. Caesarean section 2. Macrosomia 3. Polyhydramnios 4. Pre-eclampsia 5. Pre-term delivery	
Risk of bias assessment(45)						
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**
Low risk	Unclear risk Comment: precise mechanism of concealment not clear.	Low risk Comments: investigators and participants were not aware of the intervention participants received	Low risk	Low risk	Low risk	Low risk
Study: Jamilian, 2018 (47)						
Design		**Participants**	**Interventions compared**		**Reported outcomes**	
Randomized Double-blind Placebo-controlled Single centered Funding information: provided		Diagnosis: GDM Gestational age of GDM diagnosis: 24-28 week Recruited 18-40-year old's	Three interventions: 1. Probiotic: 8 x10^9 CFU/g 2. Vitamin D3: every 2 weeks plus 8 x 10^9 CFU/g probiotic		1. Caesarean section 2. Macrosomia 3. Polyhydramnios 4. Pre-eclampsia 5. Pre-term delivery	

Ethical clearance: obtained Trial ID: IRCT201706075623N119		Randomized (n) = 90 Mean age: 30 years Consent: obtained. Country: Iran		3. Placebo Duration of intervention: 6 weeks.		
Risk of bias assessment(45)						
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**
Low risk	Unclear risk Comment: precise mechanism of concealment not clear.	Unclear risk Comment: it is not clear how study personnel were blinded	Low risk	Low risk	Low risk	Low risk
Study: Jamilian, 2019 (49)						
Design		**Participants**		**Interventions compared**		**Reported outcomes**
Randomized Double-blind Placebo-controlled Single centered Funding information: provided Ethical clearance: obtained Trial ID: IRCT201704225623N109		Diagnosis: GDM Gestational age of GDM diagnosis: 24-28 week Recruited 18-40-year old's Randomized (n) = 60 Mean age: 28.4 years Consent: obtained. Country: Iran		Two interventions: 1. Vitamin D: 200 IU along with 100 mg magnesium, 4 mg zinc, 400 mg calcium twice daily 2. Placebo Duration of intervention: 6 weeks.		1. Caesarean section 2. Macrosomia 3. Polyhydramnios 4. Pre-eclampsia 5. Pre-term delivery
Risk of bias assessment(45)						
Random sequence generation	**Allocation concealment (selection bias)**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting (reporting bias)**	**Other bias**

(selection bias)		**(performance bias) All outcomes**	**(detection bias) All outcomes**	**(attrition bias) All outcomes**		
Low risk	Unclear risk Comment: precise mechanism of concealment not clear.	Low risk	Low risk	Low risk	Low risk	Low risk
Study: Karamali, 2016 (46)						
Design		**Participants**		**Interventions compared**		**Reported outcomes**
Randomized Double-blind Placebo-controlled Multicentric Funding information: provided Ethical clearance: obtained Trial ID: IRCT201407115623N23		Diagnosis: GDM Gestational age of GDM diagnosis: 24-28 week Recruited 18-40-year old's Randomized (n) = 60 Mean age: 30.15 years Consent: obtained. Country: Iran		Two interventions: 1. Vitamin D3: 50000 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 everyday Duration of intervention: 6 weeks.		1. Caesarean section 2. Macrosomia 3. Polyhydramnios 4. Pre-eclampsia 5. Pre-term delivery
Risk of bias assessment(45)						
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**
Low risk	Unclear risk Comment: precise mechanism of concealment not clear.	Low risk	Low risk	Low risk	Low risk	Low risk

Study: Razavi, 2017 (48)						
Design		**Participants**		**Interventions compared**		**Reported outcomes**
Randomized Double-blind Placebo-controlled Single centric(51) Funding information: provided Ethical clearance: obtained Trial ID: IRCT201701305623N106		Diagnosis: GDM Gestational age of GDM diagnosis: 24-28 week Recruited 18-40-year old's Randomized (n) = 120 Mean age: 29.67 years Consent: obtained. Country: Iran		Four interventions: 1. Vitamin D: 50000 IU two weekly and placebo for omega-3 fatty acids two times a day 2. Vitamin D: 50,000 IU two weekly plus 1000 mg omega-3 fatty acids two times a day 3. 1000 mg omega-3 fatty acids two times a day and placebo for vitamin D two weekly 4. Placebo Duration of intervention: 6 weeks.		1. Caesarean section 2. Macrosomia 3. Polyhydramnios 4. Pre-eclampsia 5. Pre-term delivery
Risk of bias assessment(45)						
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**
Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 2 Sensitivity analysis (by dropping one trial for every meta-analysis)							
Outcome	**Dropped study**		**RR (95% CI)**		**p-value**	**Heterogeneity**	
	Author	**Year**	**RE model**	**FE model**		**I^2 statistics (%)**	**P-value of Cochranes Q**
Caesarean section	Asemi(50)	2015	0.53 (0.36,0.78)	0.53 (0.36,0.78)	0.001*	0%	0.470
	Jamilian(47)	2018	0.61 (0.41,0.90)	0.62 (0.44,0.87)	0.012*	19%	0.295
	Jamilian(49)	2019	0.62 (0.44,0.88)	0.63 (0.45,0.87)	0.008*	12.6%	0.329
	Karamali(46)	2016	0.69 (0.48,0.97)	0.69 (0.48,0.97)	0.033*	0%	0.708
	Razavi(48)	2017	0.57 (0.40,0.80)	0.57 (0.40,0.80)	0.001*	0%	0.395
Pre-term delivery	Asemi(50)	2015	0.65 (0.15,2.73)	0.65 (0.15,2.73)	0.552	0%	0.698
	Jamilian(47)	2018	0.66 (0.16,2.79)	0.66 (0.16,2.79)	0.572	0%	0.711
	Jamilian(49)	2019	0.65 (0.15,2.75)	0.65 (0.15,2.75)	0.559	0%	0.703
	Karamali(46)	2016	0.33 (0.07,1.61)	0.33 (0.07,1.61)	0.170	0%	1.000
	Razavi(48)	2017	0.65 (0.15,2.75)	0.65 (0.15,2.75)	0.559	0%	0.703
Pre-eclampsia	Asemi(50)	2015	0.60 (0.25,1.45)	0.60 (0.25,1.45)	0.258	0%	0.816
	Jamilian(47)	2018	0.70 (0.25,1.92)	0.70 (0.25,1.92)	0.482	0%	0.893
	Jamilian(49)	2019	0.55 (0.21,1.47)	0.55 (0.21,1.47)	0.233	0%	0.799
	Karamali(46)	2016	0.60 (0.25,1.46)	0.60 (0.25,1.46)	0.261	0%	0.820
	Razavi(48)	2017	0.45 (0.16,1.25)	0.45 (0.16,1.25)	0.127	0%	0.957
Polyhydramnios	Asemi(50)	2015	0.48 (0.18,1.26)	0.48 (0.18,1.26)	0.136	0%	0.740
	Jamilian(47)	2018	0.39 (0.13,1.19)	0.39 (0.13,1.19)	0.099	0%	0.557
	Jamilian(49)	2019	0.40 (0.15,1.09)	0.40 (0.15,1.09)	0.072	0%	0.557
	Karamali(46)	2016	0.49 (0.18,1.37)	0.49 (0.18,1.37)	0.175	0%	0.677
	Razavi(48)	2017	0.32 (0.11,0.90)	0.32 (0.11,0.90)	0.032*	0%	0.795
Macrosomia	Asemi(50)	2015	0.30 (0.12,0.75)	0.30 (0.12,0.75)	0.010*	0%	0.847
	Jamilian(47)	2018	0.28 (0.10,0.78)	0.28 (0.10,0.78)	0.014*	0%	0.865
	Jamilian(49)	2019	0.33 (0.13,0.85)	0.33 (0.13,0.85)	0.021*	0%	0.889
	Karamali(46)	2016	0.34 (0.14,0.82)	0.34 (0.14,0.82)	0.017*	0%	0.959
	Razavi(48)	2017	0.27 (0.10,0.75)	0.27 (0.10,0.75)	0.012*	0%	0.882

*p-value <0.05
Abbreviations: RE: random-effect; FE: fixed-effect

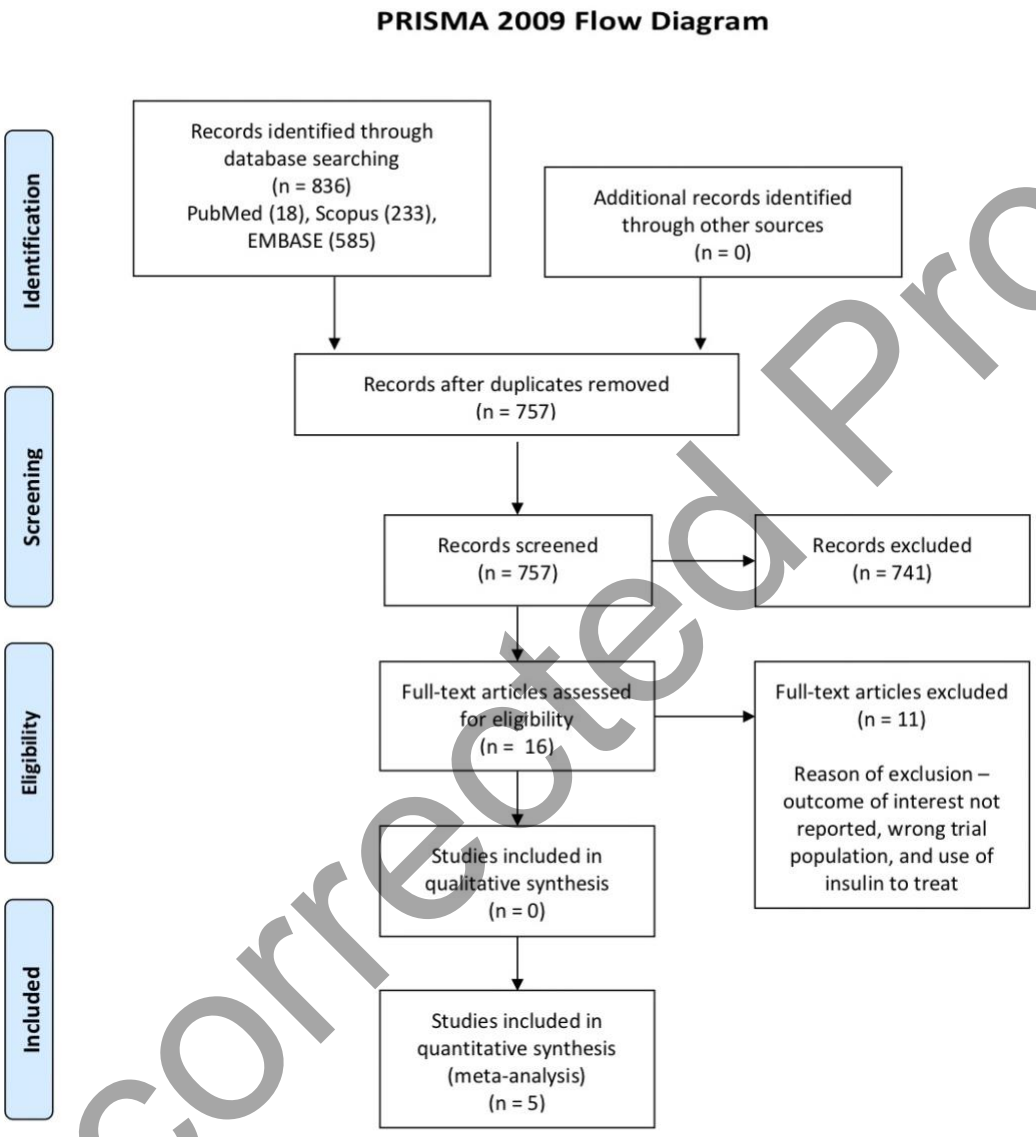

Figure 1. PRISMA 2009 Flow Diagram (From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097)

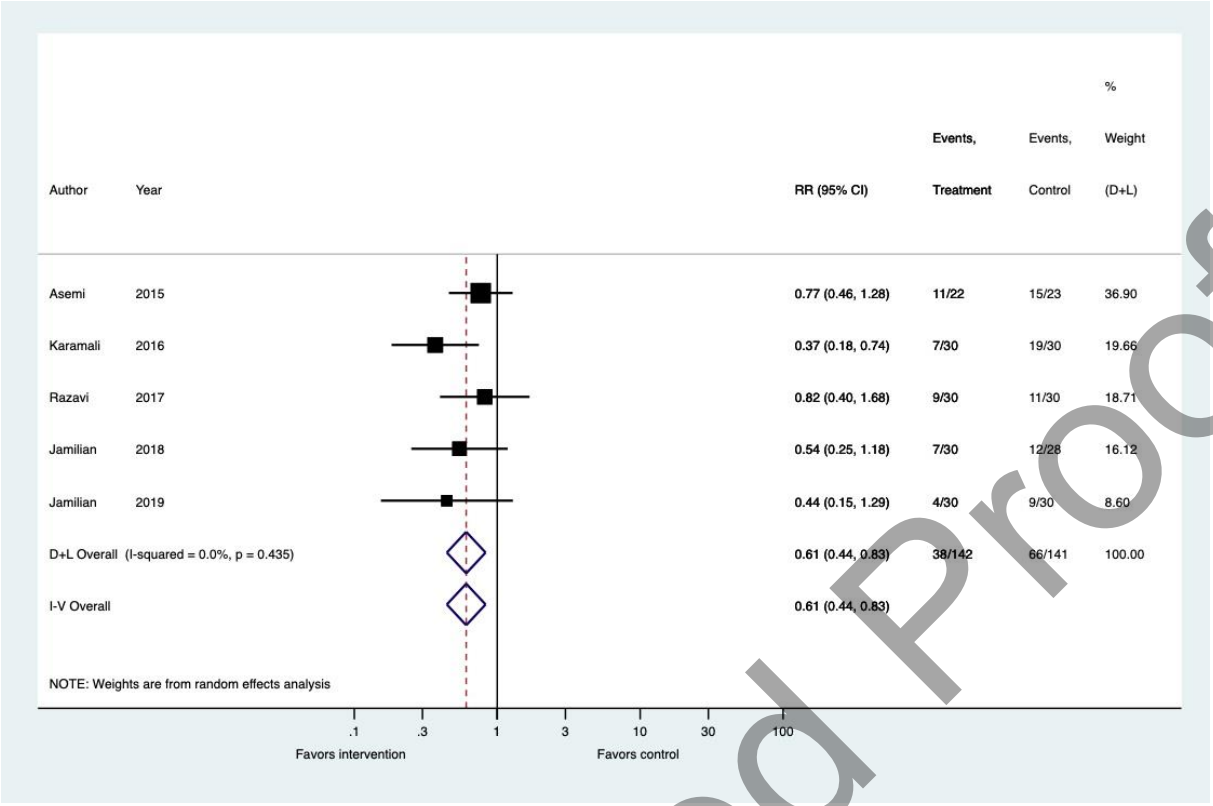

Figure 2. Forest plot: Comparison between vitamin D supplemented group and placebo for the outcome cesarean section

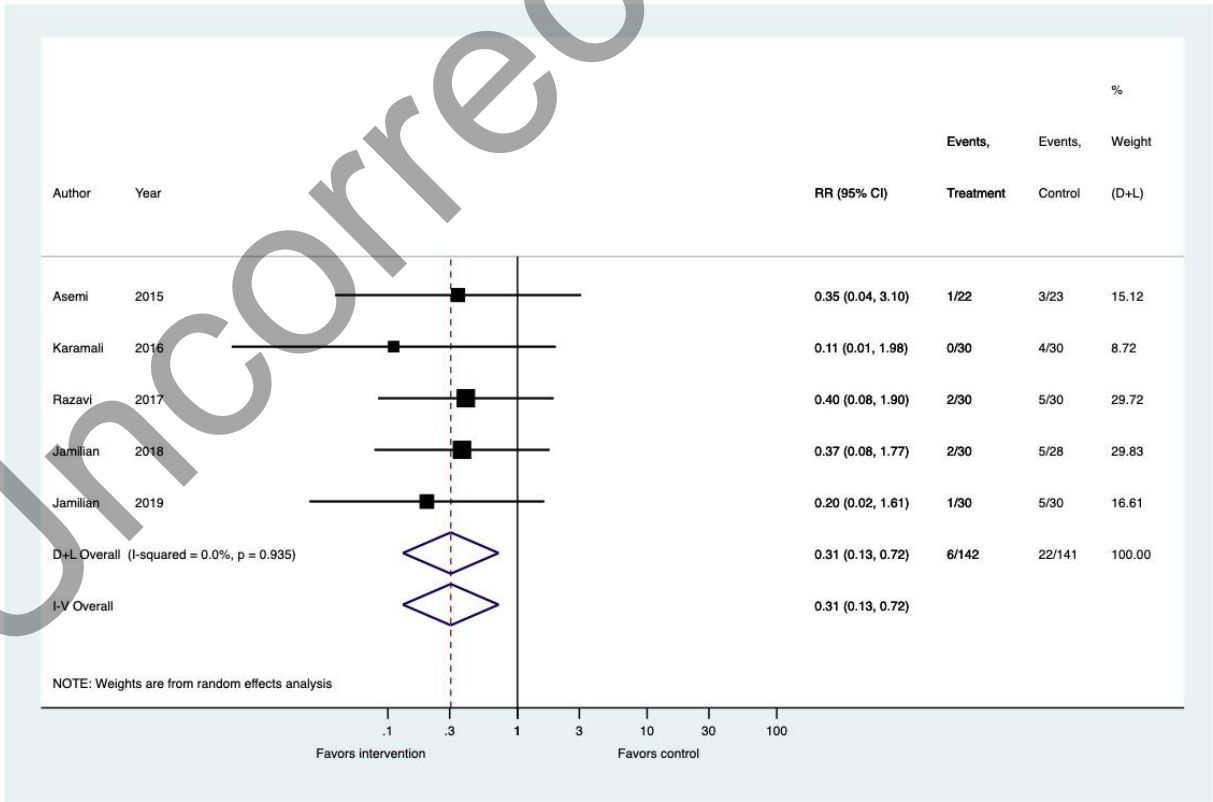

Figure 3. Forest plot: Comparison between vitamin D supplemented group and placebo for the outcome macrosomia

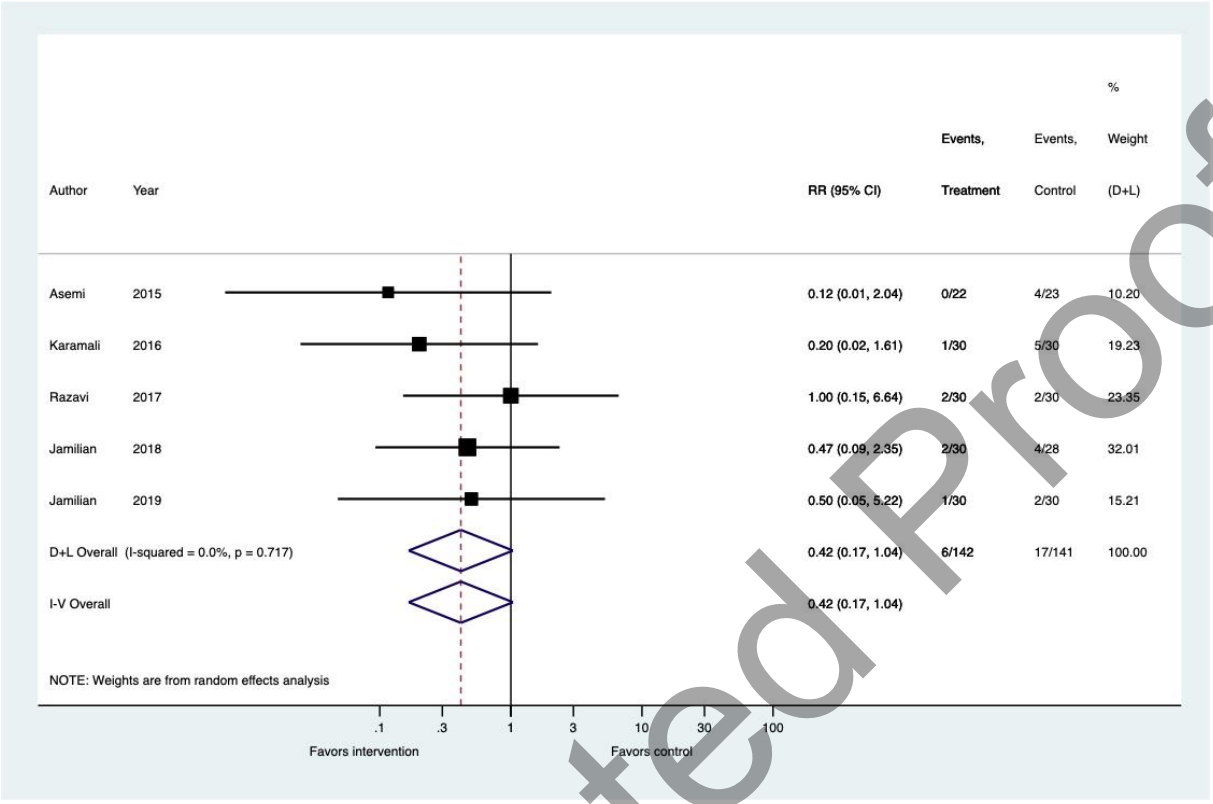

Figure 4. Forest plot: Comparison between vitamin D supplemented group and placebo for the outcome polyhydramnios

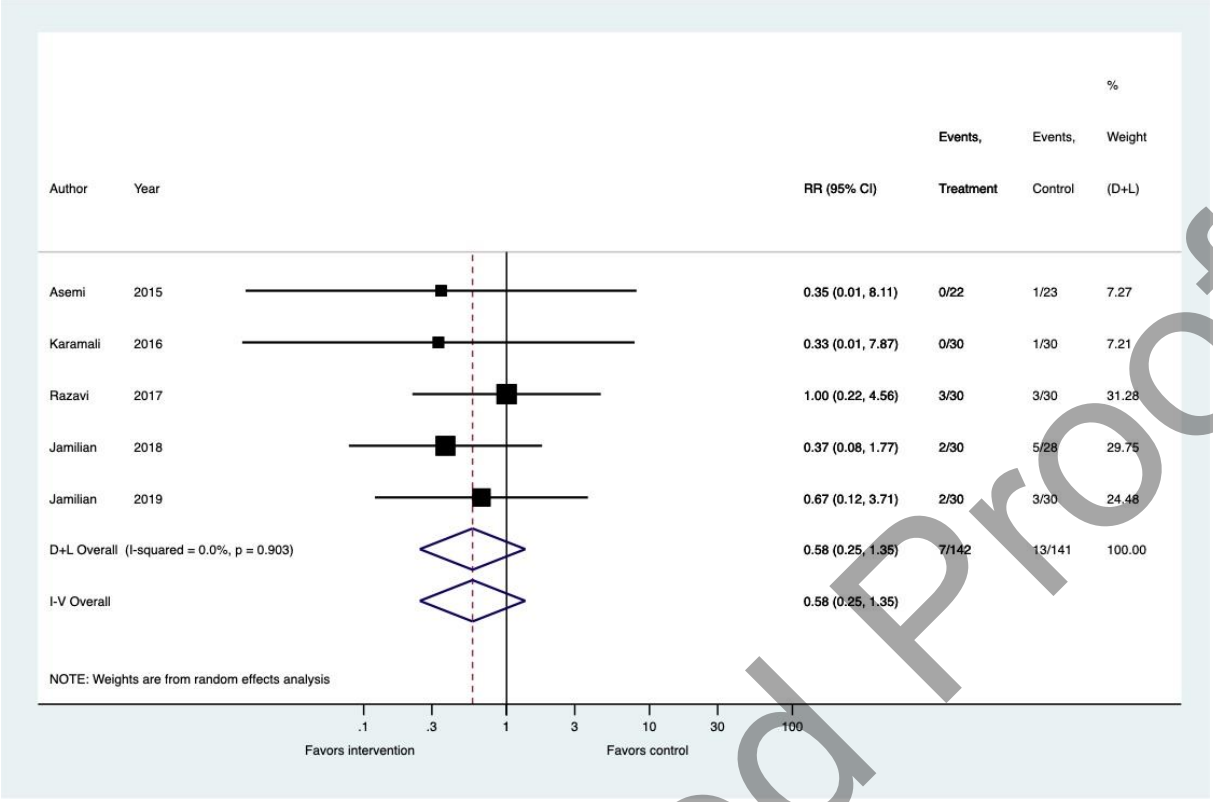

Figure 5. Forest plot: Comparison between vitamin D supplemented group and placebo for the outcome pre-eclampsia

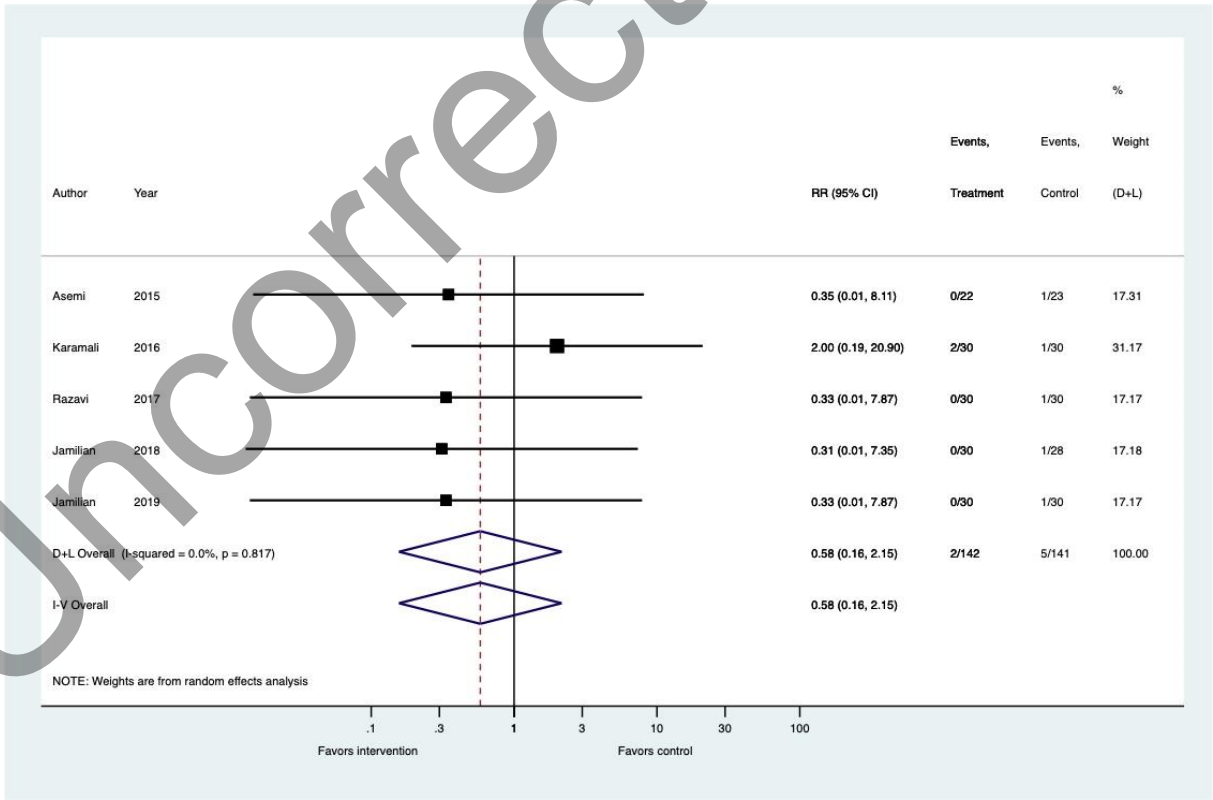

Figure 6. Forest plot: Comparison between vitamin D supplemented group and placebo for the outcome pre-term delivery