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Participant attrition and perinatal outcomes in prenatal vitamin D supplemented gestational diabetes mellitus patients in Asia: A meta-analysis

Sumanta Saha, Sujata Saha

Abstract

BACKGROUND

The role of vitamin D supplementation in gestational diabetes mellitus (GDM) patients is not clear.

AIM

This review determines the burden and risk of post-randomization GDM patient attrition from vitamin D supplemented arms of randomized controlled trials (RCT). It additionally contrasts nutritional supplements' effect on fasting blood glucose (FPG) levels and perinatal outcomes in these RCTs.

METHODS

These RCTs were searched in the PubMed, Embase, and Scopus databases. Random-effect prevalence and pairwise meta-analysis ensued for the primary objective. Fixed-effect network meta-analyses transpired for the secondary goals. All analyses transpired in Stata software, and statistical significance was determined at $p<0.05$.

RESULTS

13 RCTs from Iran and China were reviewed. The participant attrition burden in vitamin D recipients was 6% (95%CI: 0.03, 0.10), and its risk didn't vary from its non-

recipients. Vitamin D and calcium co-supplementation reduced the cesarean section incidence in GDM patients (risk ratio (RR): 0.37; 95%CI: 0.18, 0.74). The hyperbilirubinemia or hospitalization risk in their newborns decreased with vitamin D supplementation (RR: 0.47; 95%CI: 0.27, 0.83) irrespective of if it was given with calcium (RR: 0.35; 95%CI: 0.16, 0.77) or omega-3 fatty acids (RR: 0.25; 95%CI: 0.08, 0.77). Vitamin D and probiotics co-supplementation decreased newborn hyperbilirubinemia risk (RR: 0.28; 95%CI: 0.09, 0.91). FPG levels and macrosomia risk did not vary across interventions.

CONCLUSION

In RCTs supplementing vitamin D alone or as a co-supplement in GDM patients, the participant attrition burden and the risk of cesarean section, newborn hyperbilirubinemia, and newborn hospitalization were low.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a condition of glucose intolerance that is detected or diagnosed for the first-time during pregnancy. The prevalence of GDM in pregnancy is between 4-18%, depending on the diagnostic criteria used.[1] The treatment of GDM is crucial as it can cause perinatal complications like cesarean section (CS) in the mother and macrosomia in her newborn.[2] The benefits of standard GDM care with medical nutrition, lifestyle modification, and self-blood glucose monitoring are inconsistent across different treatment outcomes. For example, it decreases macrosomia risk but not the CS occurrence compared to no GDM care recipients.[3] Therefore, researchers have contemporarily investigated the role of standard GDM care adjuncts for better perinatal outcomes. In this regard, vitamin D has drawn substantial attention due to the plausible association of its deficiency and GDM.[4] Although several randomized controlled trials (RCT)[5] have tested the vitamin D efficacy in GDM patients, the burden and risk of post-randomization participant attrition from vitamin D

supplemented arms of these trials remain unclear. Notably, participant attrition happens even in the adequately conducted RCTs.[6] Besides, the efficacy of vitamin D, its co-supplements, and other supplements included in these trials, remain unclear. Existing meta-analyses have compared how vitamin D affects the occurrence of perinatal outcomes and maternal fasting blood glucose (FPG) levels.[7,8] However, these didn't distinguish how the effects of vitamin D can be differentiated from its co-supplemented forms (like with calcium) and other non-vitamin D supplements (e.g., omega-3 fatty acids) included in these trials. This meta-analysis article attempts to address these underexplored areas of perinatal medicine.

Intervention description

The fat-soluble Vitamin D hormone is available from the diet and nutritional supplements in the inactive D2 (ergocalciferol) and D3 (cholecalciferol) forms.[9,10] Cholecalciferol is further synthesized in the skin from sunlight. The pre-vitamin D undergoes hydroxylation in the liver and forms the albumin-bound circulatory 25-hydroxyvitamin D.[9,11,12] This active form of vitamin D causes calcium absorption by its action on intestine and kidneys.[10] The physiologic role of vitamin D in pregnancy occurs *via* its binding to its receptors in the uteroplacental tissue.[9,12] The dietary allowance and the tolerable upper limit of vitamin D in pregnancy are 600 and 4000IU, respectively.[9]

The vitamin D supplementation effects on GDM mothers and their neonates have been tested in several RCTs. Commonly tested oral dosages of vitamin D are 200-500 IU daily[13,14] or 50,000 IU 2-3 wkly.[15–18] While some RCTs supplemented vitamin D as a mono-supplement, others co-supplemented it with zinc, calcium, and magnesium.[14,16]

Objective

This review aims to determine the burden and risk of post-randomization GDM patient attrition from vitamin D supplemented arms of RCTs. Additionally, it determines the changes in FPG levels and risk of different perinatal outcomes (neonatal hyperbilirubinemia, newborn hospitalization, microsomia, and CS) across nutritional supplements tested in these RCTs.

MATERIALS AND METHODS

Registration and reporting

A pre-published protocol exists for this review, and it's registered in the PROSPERO (CRD42020180634).[19,20] The preliminary findings of this review were presented in a conference.[21] This report adheres to The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement (Supplementary Table 1).[22]

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Inclusion criteria

Trial design: Parallel arm RCTs of any duration.

Trial population: GDM patients of any age irrespective of their gestational age and previous GDM history.

Intervention arm/s: Prenatal vitamin D or its co-supplemented form with other nutrients orally.

Comparator arm: No nutritional supplements or placebo and/or nutritional supplement that doesn't contain vitamin D received prenatally.

Primary outcome: GDM patients leaving the trial post-randomization during the intervention period. The participants excluded from analysis by trialists were not the outcome of interest.

Secondary outcomes (post-nutrient-supplementation outcomes):

Mean FPG levels and its standard deviation and CS frequency.

Macrosomia, hyperbilirubinemia, and hospitalization of the newborns.

The diagnosis and management of GDM and the dosages and regimen of the nutritional supplements got accepted as per the trialists.

Exclusion criteria

Study designs other than that stated above. E.g., crossover study, observational study, *etc.*

Non-GDM type of diabetes like type 1 and type 2 diabetes.

Data Source

The title and abstract of the articles published in the English language were searched in PubMed, Embase, and Scopus databases irrespective of the date of publication and geographic boundary. Additionally, the bibliographies of articles included in this review got searched. The search string used to search in the PubMed was composed of the following words and phrases- "vitamin D" OR calciferol OR "vitamin D2" OR ergocalciferol OR "vitamin D3" OR cholecalciferol AND gdm OR "gestational diabetes." Identical search strings were used in the remaining databases. The complete search string with their electronic links, when available, are presented in Table S2.

Study selection and data abstraction

After uploading the retrieved citations to a reference handling software, the title and abstract of the articles got skimmed against the above eligibility criteria. Full-text reading transpired when articles appeared eligible or dubious for inclusion in this review. Figure 1 depicts the reasons for the elimination of articles read in full text. Salient details abstraction about the trials (including its registration number and country of conduct), participants, interventions tested in respective treatment arms, and the outcomes of interest transpired.

Risk of bias (RoB) evaluation

Using the Cochrane *RoB* tool for RCTs, the following *RoB* components of the reviewed trials got evaluated.[23] The randomization method and successive allocation concealment method of interventions to different treatment arm participants was used to judge the selection bias. Utilizing the blinding mechanism used for trial personnel and participants and that of outcome assessors, performance and detection bias evaluation happened, respectively. The attrition bias risk evaluation transpired by comparing the frequency and reason of missing outcome data across intervention arms. By comparing trial findings with the pre-stated intentions of trialists, the risk of reporting bias got assessed. Any other bias besides those mentioned above got classified as miscellaneous bias.

Review authors' role

The review authors performed the database search, study selection, data abstraction, and *RoB* assessment independently and resolved any conflict in an opinion by discourse. A third-party opinion or contact with the trialists was not required.

Analysis

Prevalence meta-analysis

The overall prevalence of post-randomization participant attrition from the vitamin D supplemented arms was estimated using random-effect (DerSimonian and Laird) prevalence meta-analysis (exact binomial method). Trials with zero numerators, when all participants followed up until the end of the trial period, didn't get included in the analysis.

Pairwise meta-analysis

A random effect pairwise meta-analysis model (DerSimonian and Laird) contrasted the participant attrition risk between vitamin D recipients and non-recipients and determined the summary effect in risk ratio (RR). When any cell of the 2x2 table had no event, 0.5 got added to all cells. Forest plots were used to present the results of prevalence and pairwise meta-analysis.

Statistical heterogeneity evaluation

Heterogeneity was determined using Chi^2 statistics (statistical significance determined at $p<0.1$) and successively quantified using the I^2 statistics (at values 25, 50, and 75% heterogeneity were classified as low, moderate, and high, respectively)[24]

Supplementary analysis (network meta-analysis (NMA))

A frequentist method NMA ensued for each outcome to determine the relative efficacy across various supplements tested in the reviewed trials. For FPG, the weighted mean difference was estimated, and its values got included in mg/dL (FPG values in mmol/L got converted into mg/dL). A fixed-effect NMA ensued for categorical outcomes (effect size estimated in RR) due to the absence of freedom for heterogeneity in respective models. An augmentation method was used when these binomial outcomes had zero events.

Transitivity

The NMA models don't include open-label trials to minimize the intransitivity risk. Local and global inconsistency models were used to assess inconsistency.

Network map

Utilizing network maps, a visual conceptualization of the relationship across various nutritional supplements tested in the trials transpired for each outcome. The nodes represent the intervention types received, and it enlarges with the increase in sample size receiving these. The node connectors represent the trials testing the interventions represented by the nodes, and it thickens as the no of trials increases.

League tables and intervention ranking

The effect sizes and their corresponding confidence interval (CI) are presented in league tables. The diagonal cells of these tables represented the interventions compared. The surface under the cumulative ranking curve values got utilized to predict the best supplement for outcomes with statistically significant effect sizes.

Subgroup analysis

Subgroup analysis and meta-regression were not applicable as the heterogeneity was not high in the prevalence and pairwise meta-analysis.

Publication bias

Small study effect assessment for the pairwise meta-analysis ensued using funnel plot and Egger's test. The risk of bias across studies incorporated in the NMA models occurred by assessing for selective reporting that deviates from the pre-stated notions.[25]

Sensitivity analysis

The prevalence and pairwise meta-analysis iteration happened by dropping each study every time the analysis was repeated and by using a fixed-effect model, respectively.

Certainty assessment

For statistically significant meta-analysis results, the Grading of Recommendations Assessment, Development, and Evaluation approach[26] was used to determine the evidence quality.

Analytic tools

The metaprop, meta, and network packages of Stata statistical software (version 16) were used for the prevalence, pairwise and network meta-analysis, respectively. The statistical significance was determined at p<0.05 and 95%CI.

RESULTS

Scope of this review

The database search retrieved 1357 citations (PubMed: 547; Embase: 384; Scopus: 426) (Figure 1). The last date of the search was 04-July-2021. Five articles read in full text got excluded.[18,27–30] Additional searches didn't produce any new articles. The review included 13 publications with 1,109 GDM patients' data from Iran[14–17,31–37] and China.[13,38] The salient features of these trials are presented in Table 1.

RoB evaluation

The trials were primarily at low risk of bias except one at high risk of bias (due to lack of blinding of study personnel and participants) (Table 2).[34]

Meta-analysis findings

Prevalence and pairwise meta-analysis

The pooled prevalence of participant attrition among vitamin D recipients was 6% (95%CI: 0.03, 0.10, I^2: 38.04%) (Figure 2), and its risk didn't vary from non-vitamin D recipients (Figure 3). Although the funnel plot (Figure 4) appeared somewhat asymmetrical, Egger's test didn't suggest any small study effect (P = 0.6602).

NMA

Figure 5-9 depicts the network maps. The maps revealed a lack of direct comparison between any supplement and following nutrients co-supplemented with vitamin D-calcium or magnesium-zinc-calcium combination or evening prime rose oil. The global and local inconsistency tests for any of the outcomes were not suggestive of any inconsistency. The league tables are shown in table 3-4. Vitamin D (RR: 0.47; 95%CI: 0.27, 0.83) and its co-supplementation with probiotic (RR: 0.28; 95%CI: 0.09, 0.91), omega-3 fatty acids (RR: 0.25; 95%CI: 0.08,0.77), and calcium (RR: 0.35; 95%CI: 0.16, 0.77) decreased the risk of newborn hyperbilirubinemia. Vitamin D (RR: 0.47; 95%CI:

0.27, 0.83) and its co-supplementation with omega-3 fatty acids (RR: 0.25; 95%CI: 0.08, 0.77) and calcium (RR: 0.35; 95%CI: 0.16, 0.77) reduced the risk of newborn hospitalization. The incidence of CS in GDM patients was lower with vitamin D and calcium co-supplementation (RR: 0.37; 95%CI: 0.18, 0.74). Vitamin D and omega-3 fatty acid co-supplementation in GDM patients decreased the risk of hyperbilirubinemia (RR: 0.30; 95%CI: 0.09, 0.98) and hospitalization (RR: 0.30; 95%CI: 0.09, 0.98) in their newborns compared to omega-3 supplementation alone.

The surface under the cumulative ranking curve values suggested vitamin D and calcium co-supplementation in GDM patients as the best supplement for reducing the CS requirement, and vitamin D and omega-3 fatty acids co-supplementation as the best supplement for reducing the risk of hospitalization and hyperbilirubinemia in their newborns (Table 5). The macrosomia risk and FPG levels (league table not shown) didn't vary among the interventions.

RoB across studies

Evaluation of *RoB* across studies suggests that the trials primarily adhered to their pre-stated analytic notions.

Sensitivity analysis

On repeating the prevalence meta-analysis by dropping one study each time, the prevalence ranged between 5-8%. The pairwise meta-analysis findings were identical to the preliminary model when a fixed-effect model-based iteration occurred.

DISCUSSION

Overall, this review included 13 publications sourcing data from 1,109 GDM patients from Iran and China. The risk of bias across the trials was primarily low except for one with a high risk of bias component. The burden of attrition of GDM patients from the vitamin D supplemented arms post-randomization was 6%, and this risk didn't vary from GDM patients who didn't receive the supplement. Vitamin D and calcium co-supplementation benefitted the GDM patient (the CS incidence) and her neonate (decreased hyperbilirubinemia and hospitalization risk). Vitamin D alone and its

omega-3 fatty acid added form both reduced the newborn's risk of hyperbilirubinemia and hospitalization. For these outcomes, the co-supplementation of vitamin D and omega-3 fatty acids was superior to the omega-3 fatty acids alone. Combining vitamin D with probiotics was effective in reducing the risk of newborn hyperbilirubinemia.

Quality of evidence

Using the Grading of Recommendations Assessment, Development, and Evaluation approach,[26] the NMA generated evidence was double downgraded to low-quality. This decision stood on facts that the statistically significant findings are unlikely to be generalizable as study participants chiefly sourced from Iran, a fixed-effect model NMA was used for the categorical outcomes, and the trials had few unclear risks of bias components.

Comparison with existing literature

Regarding the prevalence of participant attrition, best known to these authors, no literature is available to contrast it with the findings of this review, perhaps due to its conceptual novelty. Concerning the perinatal outcomes, existing reviews suggested that vitamin D supplementation decreased the risk of CS, macrosomia, neonatal hyperbilirubinemia, and newborn hospitalization.[8,39] However, unlike this paper's findings, these reviews[8,39] didn't disentangle how the perinatal outcomes vary across vitamin D, its co-supplemented forms, and other (non-vitamin D) supplements tested in these trials.

Strengths and weaknesses

The key strength of this review is its incorporation of RCTs only, the highest level of epidemiological evidence. The intransitivity risk in the NMA models is perhaps low due to the exclusion of the trial at a high risk of bias component. Furthermore, beyond reviewing post-randomization GDM patients' attrition burden from vitamin D supplemented trial arm/s and its risk, this is plausibly the first study that attempted to disentangle the efficacy of vitamin D and its co-supplemented forms in GDM patients.

Despite these strengths, this study also has few limitations. This review couldn't incorporate non-English language publications (if any) as the review authors are

competent in handling publications in the English language only. The anticipated generalizability of the evidence generated in this study is low due to the homogenous nature of the study population. Although the prevalence meta-analysis estimate appeared weak due to its inclusion of a trial with a high risk of bias component, the sensitivity analysis didn't observe any fluctuation upon excluding the trial from the model.

Implications

The low prevalence of post-randomization attrition of GDM patients from the vitamin D supplemented intervention arms in RCTs suggests good adherence to the supplement and might encourage trialists across the globe to conduct identical efficacy trials. Given the substantial burden of vitamin D deficiency and insufficiency in Iranian pregnant females[40] and most trials included in this review were from Iran, from a public health point of view, this study's findings might help the local health authority in reviewing the scope of routine prenatal supplementation of vitamin D and its co-supplemented forms with calcium, omega-3 fatty acids, and probiotics in GDM patients.

CONCLUSION

The post-randomization attrition burden from vitamin D supplemented intervention arms is low among GDM patients. Prenatal vitamin D and its co-supplemented form with calcium, omega-3 fatty acids, and calcium each can curb certain perinatal complications' risks in GDM patients and their neonates.

FUNDING

None received.

CONFLICT OF INTEREST

None declared.

AVAILABILITY OF DATA, CODE AND OTHER MATERIALS

The data, code and other materials will be made available by the corresponding author on receiving legitimate email correspondence.

ARTICLE HIGHLIGHTS

Research background

The role of vitamin D in gestational diabetes mellitus (GDM) is not established. Several randomized controlled trials (RCT) have tested it.

Research motivation

However, the burden and risk of participant attrition from vitamin D receiving treatment arm/s of these trials stay unclear. Also, the effect of vitamin D and its co-supplemented forms and other supplements on the mother's glycemic control and perinatal outcomes remains unclear.

Research objectives

Therefore, this study aims to address these issues.

Research methods

Eligible clinical trials were retrieved by searching the PubMed, Embase, and Scopus databases. The burden and risk of participant attrition got determined by random-effect prevalence and pairwise meta-analysis, respectively. The effect of different nutritional supplements on the perinatal outcomes got estimated by fixed-effect network meta-analysis. All analysis ensued in Stata statistical software (v16).

Research results

The database search produced 13 RCTs conducted in Iran and China. The participant attrition from vitamin D treated arms was 6% (95%CI: 0.03, 0.10), and this risk didn't vary from its non-recipient arms. The cesarean section risk decreased with the combined supplementation of vitamin D and calcium (risk ratio (RR): 0.37; 95%CI: 0.18, 0.74). The vitamin D alone and its co-supplemented forms with calcium and omega-3 fatty acids decreased the risk of newborn- hyperbilirubinemia or hospitalization. The probiotics co-supplemented form of vitamin D decreased newborn hyperbilirubinemia

risk (RR: 0.28; 95%CI: 0.09, 0.91). The fasting plasma glucose levels didn't vary across the compared interventions.

Research conclusions

This study suggests that vitamin D is a relatively well-tolerated intervention in GDM patients resulting in relatively low participant attrition from RCTs testing it. Also, this study suggests that some nutritional supplements can be beneficial in reducing perinatal outcomes.

Research perspectives

Given the low burden of participant attrition from the vitamin supplemented arms of RCTs, future trialists may find the conduct of RCTs with a larger sample size reasonable to produce rigorous results.

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