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10.4103/pjog.pjog_19_23

Association of Vitamin D supplementation in pre-eclampsia: Systematic review and meta-analysis

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Abstract:

INTRODUCTION: In the Philippines, hypertensive diseases of pregnancy belong in the top three causes of maternal mortality and complicate up to 10% of pregnancy worldwide. In relation with this, proper interventions must be given during the prenatal check-up to prevent occurrence that may cause feto-maternal mortality and morbidity. During prenatal check-up, pregnant women are given vitamin and mineral supplementations. Vitamin D has an association of having a risk for preeclampsia. Receptors of Vitamin D and 1- α hydroxylase are both expressed in the decidua and trophoblast cells. The active form of Vitamin D affects the transcription and function of genes associated with angiogenesis, invasion of the placenta, and normal implantation. The mechanisms mentioned are all involved in the pathophysiology of preeclampsia.

OBJECTIVES: The primary outcome of this study is to determine the association of Vitamin D supplementation in preeclampsia. Specifically, this study aims to compare the following secondary outcomes: Maternal outcomes (complication of gestational diabetes mellitus and underwent cesarean delivery) and fetal outcomes (preterm delivery and birth weight).

METHODOLOGY: Meta-analysis and systematic review of eight randomized controlled trials.

RESULTS: Vitamin D reduced the risk of preeclampsia (risk ratio [RR] 0.45, 95% confidence interval [CI] 0.30–0.69; $P = 0.0002$). No significant difference on risk of gestational diabetes mellitus (RR 0.84, 95% CI 0.48–1.48) and risk of preterm delivery (RR 0.71, 95% CI 0.49–1.03). Results showed that newborns of mothers who had no Vitamin D supplementation had a higher birthweight ($P = 0.010$). No significant difference on cesarean section rate (RR 1.12, 95% CI 0.87–1.45).

CONCLUSION: Evidence suggests that Vitamin D supplementation can reduce the risk of preeclampsia. This study encourages obstetricians in our country to add Vitamin D supplementation as prenatal medication to prevent preeclampsia, thereby reducing maternal morbidity and mortality.

Keywords:

Preeclampsia, preeclampsia and Vitamin D, Vitamin D, Vitamin D and pregnancy

Introduction

Background of the study

In the Philippines, hypertensive diseases of pregnancy belong in the top three causes of maternal mortality and complicate up to 10% of pregnancy worldwide. In relation with this, proper interventions

must be given during the prenatal check-up to prevent occurrence that may cause feto-maternal mortality and morbidity. Preeclampsia is defined as a syndrome that affects multi-organ system which is described by proteinuria and a new onset of hypertension after 20 weeks age of gestation. Preeclampsia with severe features includes any of the following even without proteinuria: (1) ≥ 160 mmHg systolic blood pressure or ≥ 110 on 2 occasions with at least

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How to cite this article: Ong FT, Salvador FC, Salvador DA. Association of Vitamin D supplementation in pre-eclampsia: Systematic review and meta-analysis. *Philipp J Obstet Gynecol* 2023;47:17-26.

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Submitted: 07-Apr-2023

Accepted: 11-Apr-2023

Published: 30-May-2023

4 ours interval, (2) Platelet count of $<100,000/\mu\text{L}$, (3) Impaired liver function, (4) Renal insufficiency for creatinine of $>1.1 \text{ mg/dl}$ or twice elevated from the baseline, (5) Pulmonary edema, and (6) Visual or cerebral disturbances.^[1] During prenatal check-up, pregnant women are given vitamin and mineral supplementations. Deficiency in Vitamin D is commonly encountered in pregnancy. The functions of Vitamin D in the body are maintenance of normal glucose level in the blood and regulating calcium homeostasis. In the pancreatic cells, there is binding and activation of Vitamin D receptors (VDRs), which results to the regulation of the insulin release in response with the level of circulating glucose.^[2] Vitamin D has an association of having a risk for preeclampsia. Receptors of Vitamin D and 1- α hydroxylase are both expressed in the decidua and trophoblast cells.^[3,4] The active form of Vitamin D affects the transcription and function of genes associated with angiogenesis, invasion of the placenta, and normal implantation. The mechanisms mentioned are all involved in the pathophysiology of preeclampsia.^[5]

Review of related literature

Vitamin D3/cholecalciferol production is primarily dependent in photochemical conversion unlike any other vitamins produced in the body.^[6] The biosynthesis of cholecalciferol involves hydroxylation (kidney and liver) to become biologically active. In the process of isomerization, the production of Vitamin D requires the exposure to ultraviolet B rays from the sunlight in order to convert to the pro Vitamin D3 or 7-dehydrocholesterol to pre-Vitamin D3. In the liver, the isomerized Vitamin D3 is transported and converted to 25-hydroxyvitamin D3 or calcidiol through hydroxylation. The last step of hydroxylation occurs at the kidneys wherein there is a conversion to 1, 25-dihydroxyvitamin D3 (biologically active form) that can be used in the various metabolic processes of the body.^[7]

Vitamin D in pregnancy

During the first trimester, there is a two-fold increase 1, 25(OH) 2D concentrations, and the pregnancy progresses, it continues to rise then declines after delivery.^[8] Fetus relies on mother's 25-hydroxyvitamin D which crosses the placenta and activated by the fetal kidneys into its biologically active form. Higher levels of maternal Vitamin D are needed to increase the calcium absorption in the intestines in order to support the needs of maternal and fetal metabolism including the regulation of immune system during pregnancy.^[9] Several countries excluding Asia also reported decrease in the Vitamin D status was at risk of having asthma, diabetes mellitus type I and low birth weight which are all risk factors of preeclampsia. It was also noted that there has a lower risk in developing preeclampsia among women who took Vitamin D before pregnancy.^[10]

Pathogenesis of preeclampsia and Vitamin D

In preeclampsia, the uterine arteries have a faulty trophoblastic vascular modeling that causes placental hypoxia/ischemia. Placental ischemia/hypoxia is the key initiating event in preeclampsia. There is then release of placental factors into the maternal circulation causing activation of the endothelial cells and systemic inflammatory response.^[11] Vitamin D has a role in placental invasion, implantation, immunology, and vascular genesis. Decrease in Vitamin D is caused by the decrease in the conversion from D2 to D3 (1,25(OH)₂D3) in the decidua and trophoblastic cells. If there is reduce D3 concentration, there is insufficient activation of VDR transcriptional activity resulting in insufficient expression of human leukocyte antigen genes within the extravillous trophoblasts cells.^[12] The defective trophoblastic invasion is due to the increase of the cytokine tumor necrosis factor (TNF)- α (pro-inflammatory) and the decrease of the interleukin 10 (IL-10).^[13] Vitamin D was reported to act by the downregulation of the TNF- α and upregulation of the IL-10. Vitamin D is also important in stabilizing the endothelium through nongenomic mechanisms.^[14]

Mode of delivery

VDRs are present in the human's skeletal muscle.^[15] It also affects muscle strength by influencing cell proliferation, differentiation, and size of the muscle fiber. Vitamin D helps to prevent degradation of muscles by preventing fatty degeneration, insulin resistance, and arachidonic acid mobilization. By this process, it has a role in the muscle function efficiency that is distinct from the role of calcium contractility.^[16] Vitamin D deficient pregnant women have 2-fold increase of primary cesarean section rate.^[17] There are also some studies showed the association of increase risk for cesarean delivery and deficiency of Vitamin D.^[18,19]

Diabetes mellitus

Supplementation of Vitamin D can improve glucose tolerance and sensitivity of insulin.^[20] Calcitriol has been associated to have effects on the action, secretion, and synthesis of insulin.^[21] Some studies revealed the benefits of Vitamin D supplementation on diabetes mellitus type II.^[22]

Fetal outcomes

Prematurity and intrauterine growth restrictions are associated with decrease in the levels of Vitamin D. Another study showed that mothers in the preterm group had lower 25 (OH) D plasma concentration in comparison to mothers in full term deliveries.^[23] Another study concluded that risk of preterm delivery was significantly decreased as the level of 25-(OH) increased to 90 nmol/L among pregnant women.^[24] Some literature reveals deficient plasma 25(OH) D was directly associated with premature delivery.^[25] Furthermore, Vitamin D supplementation among pregnant women

decreases the risk of premature delivery. There is also an increased risk of preterm delivery among Vitamin D deficient Chinese women and it was noted that multivitamin use, body mass index before pregnancy, and seasonality, can affect the Vitamin D level.^[26]

Birthweight

Vitamin D has a role in the growth of the fetus by its interaction with the parathyroid hormone and calcium homeostasis. Based on studies, deficient prenatal and postnatal Vitamin D levels effect on poor bone mineralization. Result of poor one mineralization includes newborn that are small for gestational age.^[27] It is proven that maternal Vitamin D levels are associated with fetal birthweight.^[28,29]

Rationale for the study

Preeclampsia is common among pregnant women. In our setting, calcium supplementation, multivitamins, and folic acid are given among pregnant women during their prenatal visits. According to the reviews, there is an association of Vitamin D supplementation among pregnant women which lead the researcher to investigate more on how to prevent preeclampsia.

Objectives

The primary goal of this study is to determine the association of Vitamin D supplementation among pregnant women with preeclampsia. Specifically, this study aims to compare the following secondary outcomes:

Maternal outcomes

- Underwent cesarean delivery
- Development of gestational diabetes mellitus.

Fetal outcomes

- Preterm delivery
- Birth weight.

Methodology

Types of study

Randomized controlled trials were included in this study. Observational design was not included in this study but was considered in the discussion if necessary.

Participants

All pregnant women of any gestational age, multifetal pregnancy, and pregnant women with gestational diabetes mellitus were excluded.

Interventions

Interventions include supplementation of Vitamin D among pregnant women regardless of duration and dosage. The study includes trials with Vitamin D

supplementation only or combined with other regular prenatal vitamins and minerals.

Outcome measures

The primary outcome of this study was to determine the association of Vitamin D supplementation in preeclampsia.

The secondary outcomes for association of Vitamin D supplementation among pregnant women:

Maternal outcomes

- Underwent cesarean delivery
- Development of gestational diabetes mellitus.

Fetal outcomes

- Preterm delivery
- Birth weight.

Search strategy

This study was based on systematic searches in literature databases such as Elsevier, PubMed, HERDIN, Cochrane library, and Epistemonikos. The researchers used the following computerized databases for English language publications using the terms: "Vitamin D," "Preeclampsia," "Vitamin D supplementation," "Vitamin D and Preeclampsia." The literature search included all published studies on the association of Vitamin D supplementation and preeclampsia. The Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines and flow diagram for meta-analysis were utilized in this study. Language restrictions were not applied.

Selection studies

Randomized controlled trials on Vitamin D supplementation only or combined with other regular prenatal vitamins and minerals were included. Independent reviews were done among three authors. As necessary, authors of publications were contacted if additional information were needed.

Management and data extraction

All studies utilized the Review Manager (RevMan) 5.4.1, The Cochrane Collaboration, 2020.

Risk of bias

Three authors assessed the study independently using the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). The following domains were evaluated: performance bias, detection bias, attrition bias, selection bias, selective outcome reporting, and overall bias. The classification was low, high, or unclear on each items.

Measures of treatment effect

Meta-analysis statistical analysis was done using the Review Manager Software 5.4.1. The presentation

of data using risk ratio (RR) with 95% confidence intervals (CIs) was be used for the dichotomous data. Mean difference was used to measure the outcomes between trials (continuous data).

Missing data

Every participant in the group to which they were allocated, with or without allocation intervention was included in the data analysis. For those with missing data, clarification from the authors was sought.

Assessment of heterogeneity

In assessing the statistical heterogeneity, the Tau^2 , Chi-square and I^2 statistics were used. An $I^2 < 25\%$ was considered homogenous, 25%–75% as medium and $> 75\%$ as high heterogeneity. Studies with low $I^2 < 75\%$ were considered good study. The conclusion of accuracy of estimates was difficult for $I^2 > 75\%$.

Estimation of risk difference

Review Manager Software (RevMan 5.4.1) was used for all statistical analysis in this study. Fixed and random-effects model was used to assess statistical heterogeneity. Random effects meta-analysis was used for substantial heterogeneity, to create a summary of an average treatment effect among the studies. The random-effects summary was treated as the average range of possible treatment effects. Fixed-effect meta-analysis was used for studies with the same underlying treatment effect (homogenous studies). Forest plot was provided to illustrate visual summary of analysis and graphically present estimates and CI for each study.

Assessment of reporting bias

Funnel plot asymmetry was assessed to investigate for publication bias.

Sensitivity analysis

It was conducted based on the quality of each study. A study was classified as high quality if it was assessed as having low risk of bias in allocation concealment and randomization.

Statistical analysis

The outcomes of Vitamin D supplementation in preeclampsia were analyzed using Review Manager (RevMan) 5.4.1, The Cochrane Collaboration, 2020. The significance between the groups was estimated by odd's ratio with 2 tailed 95% CI. Mantel and Haenzsel and fixed-effects model were employed on the variables. $P < 0.05$ was considered significant. Statistic value I^2 represented the degree of heterogeneity. P value for the test of heterogeneity < 0.01 was considered significantly heterogeneous between studies.

Ethical concerns

In any cases wherein full text of selected journals was not available, the plan was: authors of selected journals will be contacted via E-mail, SMS, or any online accounts.

Results

Selection process

The principal author reviewed all potential studies for inclusion against the eligibility criteria. The author examined the title, abstract, and, where necessary, the full text of studies to assess if they are eligible for inclusion.

Data collection process

The principal author and two other reviewers used a standard form to independently extract the study characteristics and outcome data from the studies. Discrepancies were checked against the original article. Disagreements in values were settled by the consensus.

Data items

The following information were collected: study design, patient characteristics such as age, gestational age, and parity, specific intervention given such as the dosage and delivery of Vitamin D supplementation or standard of care, and outcomes such as maternal outcomes (gestational diabetes mellitus), birth outcomes (cesarean delivery and preterm delivery), and fetal outcomes (birthweight).

Data analysis

Forest plots were generated using Review Manager 5.4.1 and STATA 15. The degree of heterogeneity between studies was assessed using the I^2 statistic. The I^2 statistic describes the percentage of total variation across studies that are caused by heterogeneity rather than by chance. The values of I^2 lie between 0% and 100%, where the higher the value, the more considerable the heterogeneity.

A total of 138 studies were identified for inclusion in this systematic review and meta-analysis. All were randomized controlled trials only. The search of PubMed/MEDLINE, Cochrane, and Epistemonikos provided a total of four citations. Adjusting for duplicates and removal for other reasons such as being unrelated, having different subjects (animals), different intervention (not vitamin D), different type of literature (book references or review studies), and inaccessible trial/journal done. After screening the full-text papers, 8 studies met the inclusion criteria and were included in the systematic review and meta-analysis [Figure 1].

Study characteristics

The characteristics of each study are shown in Table 1 tabulating the study location, study inclusion/exclusion criteria, blinding of studies, specific intervention given,

Table 1: Study characteristics

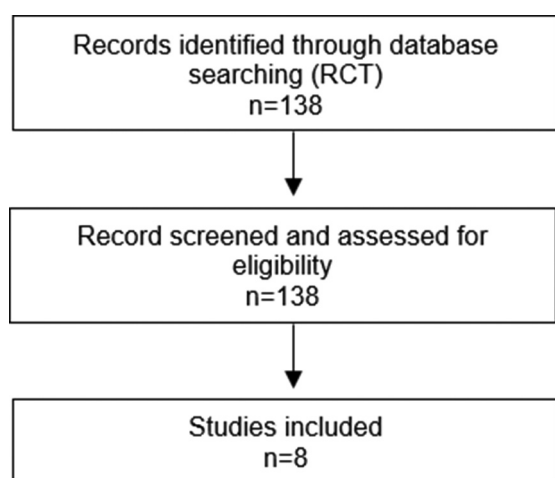
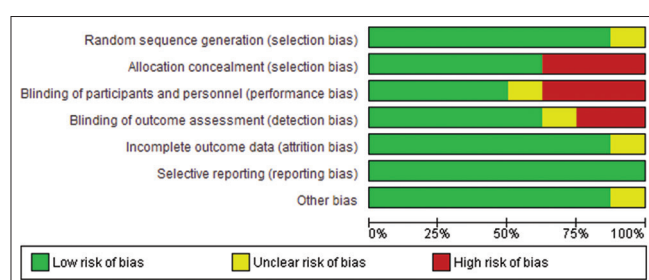
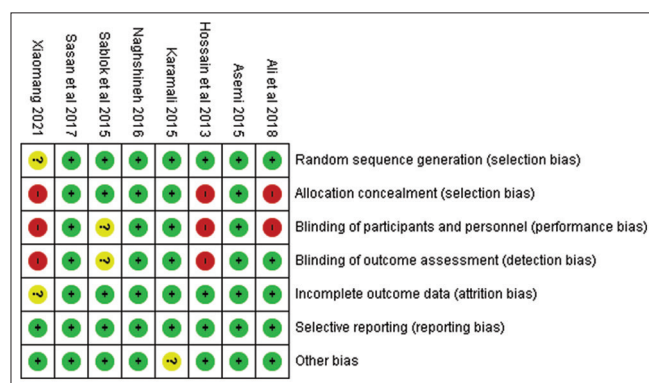
Study ID	Ali, 2019	Asemi, 2015	Hossain, 2014	Karamali, 2015	Naghshineh, 2016	Sablok, 2015	Sasan, 2017	Xiaomang, 2020
Country	Saudi Arabia	Iran	Pakistan	Iran	Iran	India	Iran	China
Study design	Parallel, open-label, RCT	Parallel, double-blind, placebo-controlled RCT	Parallel, open-label RCT	Double-blind, placebo-controlled RCT	Double-blind RCT	Double-blind RCT	Double-blind RCT	RCT
Inclusion criteria	Maternal age of 20–40 years Confirmed singleton pregnancy of <13 completed weeks of gestation at the time of consent Low risk pregnant 25(OH) D levels <25 nmol/L	Aged 18–40 years old Positive roll-over test Primigravida, who were carrying singleton pregnancy at their third trimester	≤20 weeks of gestation with a singleton pregnancy Normoglycemic and normotensive at the time of antenatal booking	Pregnant women primigravida, aged 18–40 years old and at risk for preeclampsia	Pregnant women at <16 week gestation	Primigravidae with singleton pregnancy at 14–20 weeks	Receiving prenatal care and had a history of preeclampsia in previous pregnancies, 25-hydroxy Vitamin D was equal or higher than 25 ng/mL	Pregnant women aged 20–40 years, pregnant women were singleton pregnancies
Exclusion criteria	Mothers with abnormal fetus History of hypertension Preeclampsia Recurrent miscarriages Chronic kidney disease Chronic liver disease Malignancy	Maternal severe preeclampsia Intrauterine fetal death PPROM CBR Placenta abruption Preterm delivery GDM	History of gestational diabetes Hypertension Thyroid disorder Chronic liver disease Evidence of fetal anomaly in current pregnancy	Abnormal fetal anomaly scan or were being treated with warfarin	Familial history of PTL, infection and other risk factor of PTL	Preexisting osteomalacia, known hyperparathyroidism, renal, liver dysfunction, tuberculosis, sarcoidosis	Risk of chronic hypertension before pregnancy, concurrent renal, pulmonary and cardiac diseases, immunologic diseases such as lupus	Fetal abnormalities Repeated abortions in pregnant women History of hypertension, chronic liver and kidney disease, preeclampsia, and malignant tumors
Trial arms								
Intervention	4000 IU Vitamin D3 (40 drops daily)	Multi-mineral Vitamin D supplements	400 IU/day Vitamin D3 at a daily dose of 4000 IU (10 drops daily) starting at completed 20 weeks of gestation	One oral pearl containing 50,000 IU Vitamin D3	600 IU daily of Vitamin D at 16 weeks gestation until labor	Vitamin D supplementation in dosages depending upon the level of serum 25(OH)-D levels estimated at entry into the study	50,000 IU pearl Vitamin D3 once every 2 weeks	Vitamin D: Low-dose (400 IU), middle-dose (1500 IU), high-dose (4000 IU), oral
Control	400 IU Vitamin D3/ tablet once daily	Placebo	Ferrous sulfate 200 mg, twice daily and 600 mg of calcium lactate daily	Placebo	Daily supplementation free of Vitamin D	Did not receive any supplementation of Vitamin D	Placebo	
Number of patients								
Intervention	83	23	86	30	68	108	70	Low - 134 Medium - 134 High - 138
Control	81	23	89	30	70	57	72	
Age								

Contd...

Table 1: Contd...

Study ID	Ali, 2019	Asemi, 2015	Hossain, 2014	Karamali, 2015	Naghshineh, 2016	Sablok, 2015	Sasan, 2017	Xiaomang, 2020
Intervention	29.4±4.8	25±4.2	25.96±3.13		25±3.8		32.04±5.901	Low - 28.76±3.16 Medium - 28.54±3.27 High - 28.94±3.21
Control	29.3±5.3	24.4±3.6	25.19±4.36		24.8±4.4		29.77±5.21	
Outcomes measured	Caesarean delivery, preterm delivery, miscarriage, IUGR, gestational DM, preeclampsia, Gestational age at delivery, birth weight	Caesarean delivery, gestational age at delivery, newborn's weight, newborn's length, newborn's head circumference, severe preeclampsia, gestational DM	Duration of gestation (weeks), preterm birth, gestational hypertension, preeclampsia, age, preterm delivery, abnormal GCT, small for gestational age, intrauterine fetal demise, cesarean section, birth weight, head circumference, birth length, Apgar score	Cesarean section, gestational age, preterm delivery, newborn's weight, newborn's head length, newborn's head circumference, 1-min Apgar score, 5-min Apgar score, preeclampsia rate, LBW	Preeclampsia, delivery, PTL	PTL diagnosis, gestational hypertension/ preeclampsia, gestational diabetes	Preeclampsia	Preeclampsia IUGR
Key result	Vitamin D supplementation in the deficient group reduces the risk of preeclampsia and IUGR in a dose dependant manner	Multi mineral-Vitamin D supplementation for 9-week in pregnant women at risk for preeclampsia resulted in increased newborn's length, increased circulating levels of maternal serum calcium, magnesium, zinc and Vitamin D and led to decreased maternal SBP and DBP	Maternal Vitamin D supplementation improved maternal and neonatal Vitamin D status. Improved neonatal Apgar scores, were observed in babies of mothers receiving antenatal Vitamin D supplementation	The administration of cholecalciferol supplementation for 12 weeks had favorable effects on insulin metabolism parameters, serum HDL-cholesterol and plasma TAC concentrations, while it did not affect FPG, other lipid concentrations, inflammation, oxidative stress, blood pressures, and pregnancy outcomes	Vitamin D supplementation during the third trimester of pregnancy; despite the nonsignificant association between Vitamin D supplementation and preeclampsia, reduce the risk of preeclampsia	Vitamin D supplementation reduces risk of maternal comorbidities and helps improve neonatal outcomes	The intended intervention (i.e., prescription of Vitamin D) has a protective effect against recurrent preeclampsia. Vitamin D supplementation therapy in pregnancy could help in reducing the incidence of gestational Hypertension/ preeclampsia	

RCT: Randomized controlled trial, IUGR: Intrauterine growth restriction, DM: Diabetes mellitus, PPRM: Premature preterm rupture of membrane, CBR: Completed bed rest, GDM: Gestational DM, LBW: Low birth weight, PTL: Preterm labor, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, GCT: Glucose challenge test, FPG: Fasting plasma glucose, TAC: Total antioxidant capacity, HDL: High-density lipoprotein

Figure 1: Flow diagram of studies selection process^[34-42]Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies^[34-42] (RevMan 5.4.1)Figure 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study^[34-42] (RevMan 5.4.1)

number of patients given intervention, and outcomes measured.

Risk of bias in studies [Figures 2 and 3]

Allocation (selection bias)

The subjects on all studies were randomized using a computer-generated program except for one study that was unclear and did not specify the scheme that was used. Three out of eight studies were open-label studies.

Blinding (performance and detection bias)

Three out of eight studies were open-label studies so there was no blinding of both participants and personnel.

Incomplete outcome data (attrition bias)

Seven out of eight studies has low risk of bias since the dropout rate was 0%–15% while one study was unclear and did not mention any completeness of outcome date.

Selective reporting (reporting bias)

The objectives, scope, and limitations in all studies were clearly stated and met.

Other potential sources of bias

No other potential sources of bias noted except for one study that did that did not mention if there were other concerns.

Data analysis

Primary outcome

Preeclampsia

A total of 8 studies and 1163 pregnant women were included in the analysis. Vitamin D reduced the risk of preeclampsia (RR: 0.45, 95% CI: 0.30–0.69) [Figure 4].

Secondary outcome

Gestational diabetes mellitus

A total of 5 studies and 810 pregnant women were included in the analysis. No significant difference (RR: 0.84, 95% CI: 0.48–1.48) [Figure 5].

Cesarean delivery

A total of 7 studies and 998 pregnant women were included in the analysis. No significant difference (RR: 1.12, 95% CI: 0.87–1.45) [Figure 6].

Preterm delivery

No significant difference (RR: 0.71, 95% CI: 0.49–1.03) [Figure 7].

Birthweight

Overall, the results suggest that the newborns of mothers who had no Vitamin D supplementation had a higher birthweight ($P = 0.010$) [Figure 8].

Discussion

Preeclampsia is one of the major health concerns among pregnant women in the Philippines since it is associated with adverse feto-maternal outcomes.^[30,31] This review evaluates the association of Vitamin D in preeclampsia. It includes 8 randomized control trials, six of which compared with placebo or usual prenatal medications. This meta-analysis indicates that Vitamin D supplementation during pregnancy was beneficial in reducing the risk of preeclampsia. Similar studies revealed the same results.^[32,33]

Since Vitamin D has a role in placental invasion, implantation and angiogenesis, a decrease in Vitamin D3 concentration may result in defective trophoblastic invasion. Therefore, Vitamin D is important in

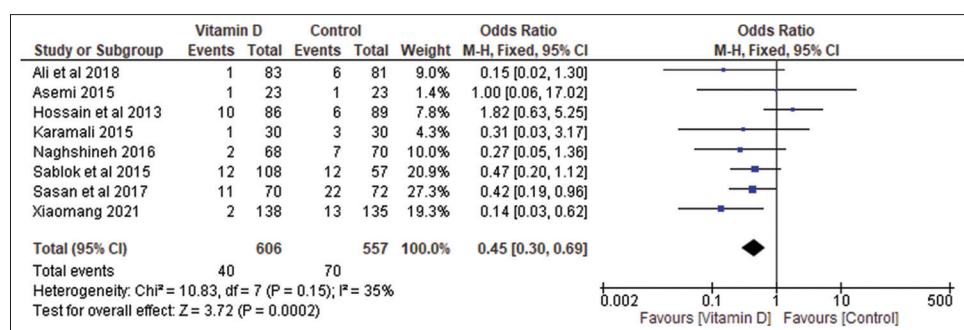


Figure 4: Forest plot of comparison: 1 Vitamin D and Control, outcome: 1.1 Preeclampsia

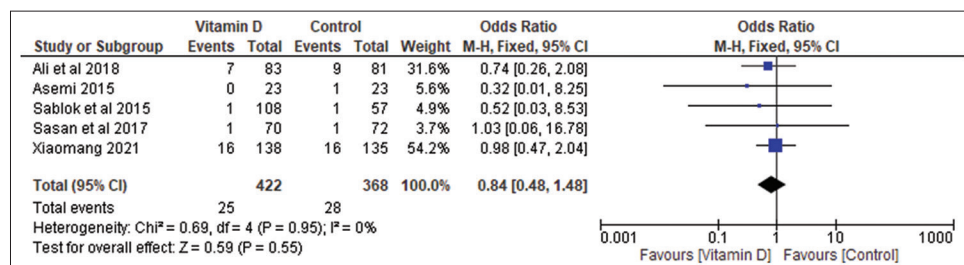


Figure 5: Forest plot of comparison: 1 Vitamin D and control, outcome: 1.3 gestational diabetes mellitus

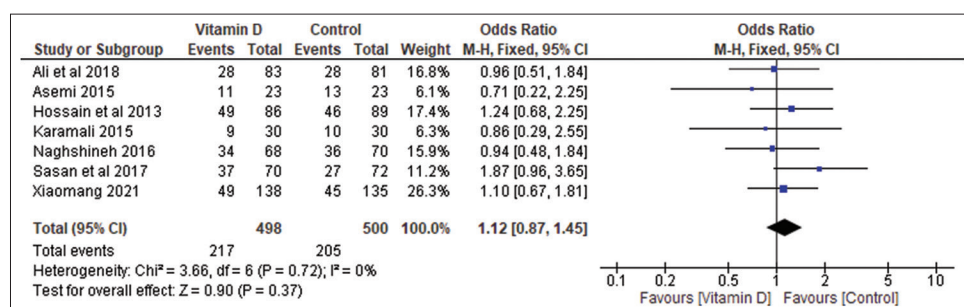


Figure 6: Forest plot of comparison: 1 Vitamin D and control, outcome: 1.2 cesarean delivery

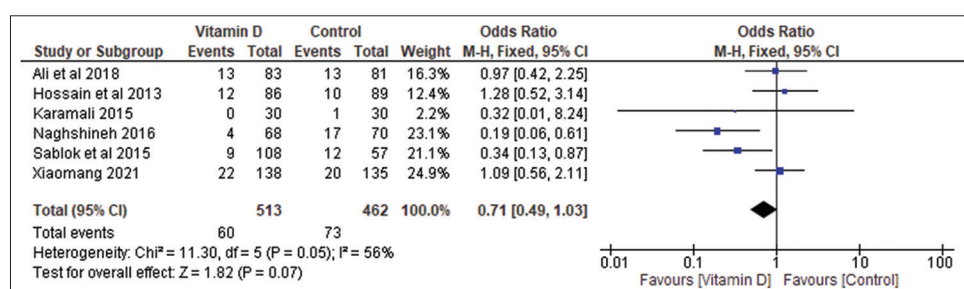


Figure 7: Forest plot of comparison: 1 Vitamin D and control, outcome: 1.4 preterm delivery

stabilizing the endothelium, thereby reducing the risk of preeclampsia. Vitamin D supplementation can be beneficial and applicable in our country since the population included were comparable to the Filipinos. The associated complications of preeclampsia include development of diabetes mellitus and preterm delivery. According to Burris and Camargo (2013),^[20] Vitamin D can improve tolerance to glucose and sensitivity to insulin. In the study of Robinson CJ, Wagner CL, Hollis BW, Baatz JE

and Johnson DD (2013),^[34] gestational diabetes mellitus and preterm deliveries were also reduced. However, in this review, there was no significant difference between the development of gestational diabetes. Maybe Vitamin D supplementation only benefits diabetes mellitus type according to some studies. According to Robinson *et al.* and Maxwell *et al.*^[28,29,43] maternal Vitamin D levels are associated with birthweight. This is secondary to its role in the growth and bone mineralization. Poor bone

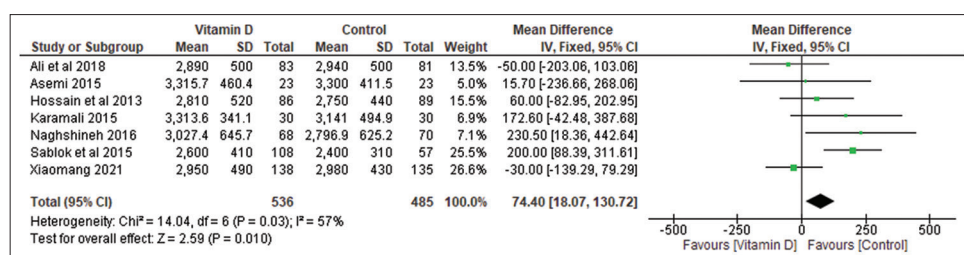


Figure 8: Forest plot of comparison: 1 Vitamin D and control, outcome: 1.5 birthweight

mineralization may result small for gestational age newborns. Based on this review, mothers who had no Vitamin D supplementation have a higher birthweight. However, those with Vitamin D supplementation have lesser birth weight but is still appropriate for gestational age. Since Vitamin D has a role in the muscle strength, mobilization, function and contractility, pregnant women who has deficient with Vitamin D has increase risk for cesarean delivery. However, in this study, there was no significant difference between cesarean section rate. The number of subjects per study can significantly affect the result. Medium heterogeneity was observed on three parameters (preeclampsia, preterm delivery, and birthweight). Supplementation regimens may be the potential sources of heterogeneity. Sensitivity analysis suggests that the quality of trials does not affect outcomes. Pregnant women in our country can benefit by adding Vitamin D supplementation in the routine prenatal medications.

Conclusion

Evidence suggests that Vitamin D supplementation can reduce the risk of preeclampsia. This study encourages obstetricians in our country to add Vitamin D supplementation as prenatal medication to prevent preeclampsia, thereby reducing maternal morbidity and mortality.

Limitations

The study has included randomized control trials only. Interventions included were the supplementation of Vitamin D among pregnant women (any age of gestation) regardless of duration and dosage. The trials included were Vitamin D supplementation only or combined with other micronutrients. Cost-effectiveness was not measured.

Recommendations

Future researchers may focus of the following:

1. Recommended dose and duration of Vitamin D supplementation
2. Cost-effectiveness.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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