

# THE EFFECT OF VITAMIN D SUPPLEMENTATION IN PREGNANT WOMAN FOR PRE-ECLAMPSIA INCIDENCE: A LITERATURE REVIEW

Tia Mella Citra, Ratih Pramuningtyas, Tri Agustina, Erna Herawati, Ayu Mayangsari, Zhela Fatin Fatiha, Aulia Nissa Rizky Hariyono

Department of Medicine, Faculty of Medicine, University of Muhammadiyah Surakarta, Indonesia

\*e-mail: [J500190030@student.ums.ac.id](mailto:J500190030@student.ums.ac.id), [ratihpramuningtyas@gmail.com](mailto:ratihpramuningtyas@gmail.com),

[triagustina@gmail.com](mailto:triagustina@gmail.com), [ernaerawati@gmail.com](mailto:ernaerawati@gmail.com), [ayumayangsari@gmail.com](mailto:ayumayangsari@gmail.com),

[zhelafatin@gmail.com](mailto:zhelafatin@gmail.com), [aulianissa@gmail.com](mailto:aulianissa@gmail.com)

\*Correspondence: [J500190030@student.ums.ac.id](mailto:J500190030@student.ums.ac.id)

*Submitted*: 05 October 2022      *Revised*: 16 October 2022      *Accepted*: 25 October 2022

**Abstract:** Pre-eclampsia was defined as hypertension after 20 weeks of gestation with evidence of maternal organ dysfunction, uteroplacental, or proteinuria. Maternal vitamin D deficiency may be with an increased risk of pre-eclampsia. Nonetheless, To assess the impact of vitamin D supplementation on the risk of pre-eclampsia, we performed a literature review. We researched Google Scholar; PubMed; Research Gate; and Science Directs using keywords ("Vitamin D" OR "Hydroxyvitamin D (25(OH)D)" OR "25(OH)D" OR "25hydroxycholecalciferol") AND ("Pregnancy" OR "Pregnant women" OR "Gestation") AND ("Clinical trial" OR "Clinical study" OR "study" OR "prospective study" OR "Randomized controlled trial" OR "RCT") from January 2006 – May 2021. A total of 4 of 19.431 articles were recorded at the identification stage by the criteria for inclusion. The articles are randomized controlled trials (RCT). A total of 329 pregnant women are given various vitamin D supplements with a dose range of 400 - 4.000 IU. Some articles combine with another vitamin (Calcium, Vitamin C+E) for a certain duration. Maternal ages range 20 years - 40 years with a gestational age of 6 to more than 32 weeks. Vitamin D can reduce the risk of pre-eclampsia in pregnant women.

**Keywords:** Vitamin D, Pregnancy, Pre-eclampsia.

## INTRODUCTION

Pre-eclampsia is a disease characterized by hypertension ( $\geq 140/90$ ) and proteinuria (300 mg/24 hours) that occurs after 20 weeks of gestation in women who were previously normotensive and has multi-factorial disorders that can cause complications such as eclampsia, liver failure, kidney failure, edema, stroke, cardiovascular disorders, metabolic disorders, prematurity, and even death. Pre-eclampsia greatly affects the condition of the mother and baby during pregnancy. The reported prevalence of pre-eclampsia is between 1.3%-10% of all pregnancies. Increased oxidative stress biomarkers are considered to be a key factor in the process of pre-eclampsia (Azami et al., 2017).

One study suggests that maternal vitamin D and calcium deficiency during pregnancy may be an independent risk factor for pre-eclampsia. In a meta-analysis study showed that pregnant women who received vitamin D supplementation in early pregnancy had a positive association and a lower risk of pre-eclampsia because vitamin D could reduce oxidative stress markers. Vitamin D can also stimulate the immune system in decidual tissue and may promote healthy placental function. The risk of pre-eclampsia is reduced by 27% among women who take 400-600 IU daily

vitamin D supplements compared to those taking no supplements.

Vitamin D deficiency is defined as a serum 25(OH)D level of less than 20 ng/ml (50 nmol/liter), while an insufficient 25(OH)D level is less than 29 ng/ml (525-725 nmol/liter) so it is necessary giving vitamin D supplementation in order to avoid the risks that may occur (Amrein et al., 2020).

The daily routine antenatal vitamin D is 400 IU while the safest maximum recommended dose for vitamin D supplementation in pregnancy is 4000 IU. Many studies conclude that high-quality randomized trials are needed to determine the recommended dose of vitamin D supplementation in pregnancy. Despite consistent published evidence regarding the achievement of optimal maternal and infant vitamin D status with antenatal supplementation at higher doses of up to 4000 IU. One study suggested that supplementation of high doses of vitamin D (4000 IU) in a vitamin D-deficient pregnant population would reduce the risk of pre-eclampsia and help achieve normal levels of vitamin D3 (Ali et al., 2019). This study aimed to assess the impact of vitamin D supplementation on the risk of pre-eclampsia.

## MATERIALS AND METHODS

This research is a literature review. PRISMA and Synthesis Without Meta-analysis guidelines were applied to analyze this literature review with the aim of

assessing the effect of vitamin D supplementation on pregnant women on the incidence of pre-eclampsia with the inclusion criteria for study selection in the

form of RCT. retrospective, retrospective cohort, case-control, and experimental exclusions for this type of Systematic Review/Literature Review study. The selected sample is a sample of pregnant women of all ages without any restrictions on gestational age, number of previous pregnancy history, and accompanying medical history. The year of publication that we use is the journal in the year published January 2006 – May 2021. The language we use is the journal in English. The final results (Outcomes) influence the journal. Effect of vitamin D supplementation on pregnant women with pre-eclampsia. Journals will be excluded by researchers. if it does not present data whose results discuss the effect of vitamin D on pregnant women in pre-eclampsia

and studies in the form of abstracts or brief reports. Researchers did not limit the intervention to related journals. Search for literature that met the inclusion criteria using PubMed, google scholar, Research Gate, and Science Directs database sources, the researchers did use the keywords ("Vitamin D" OR "Hydroxyvitamin D (25(OH)D)" OR "25(OH)D" OR "25hydroxycholecalciferol") AND ("Pregnancy" OR "Pregnant women" OR "Gestation") AND ("Clinical trial" OR "Clinical study" OR "study" OR "prospective study" OR "Randomized controlled trial" OR "RCT"). All obtained journals are exported to Microsoft excel. All data were extracted by 4 researchers. The selection of relevant studies was based on pre-determined inclusion criteria.

## RESULTS AND DISCUSSION

A total of 4 19,431 articles were found in Google scholar (17,400), PubMed (2030), research gate (100), and science direct (1). Using 4 RCT articles (n=329) for further study. A total of 329 pregnant women are given various vitamin D supplements with a dose range of 400-4.000 IU. 2 of the 4 studies used combined vitamin D with other supplements (Calcium and Vitamin C+E) with a certain duration. Maternal ages range 20 – 40 years with gestational age 6 to more than 32 weeks.

---

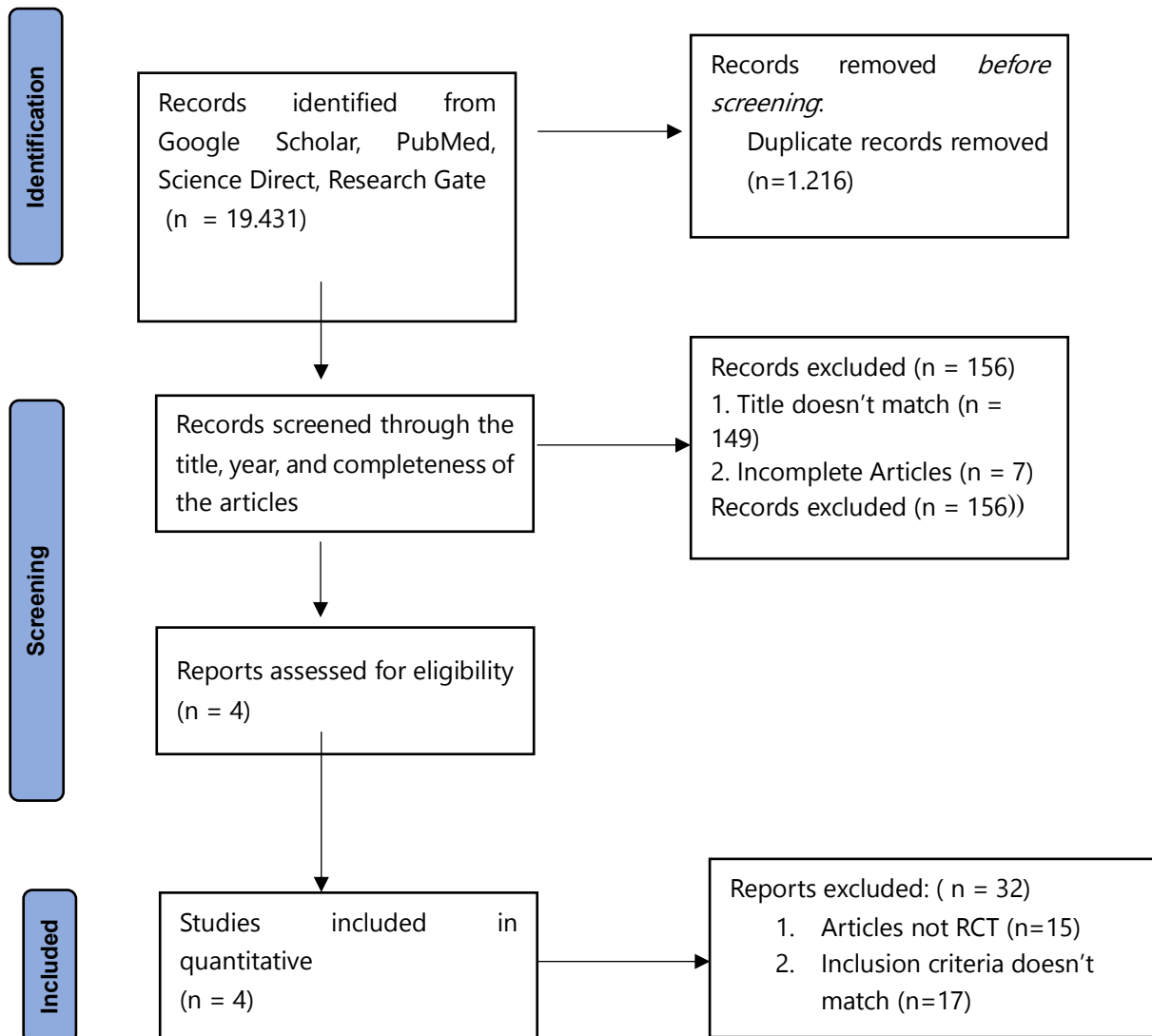


Fig. 1. PRISMA search and selection of the diagram Literature

First author (years)	Study location	Design	criteria for the studies (gestation )	INTERVENTION	STUDY GROUP	PARTICIPANT (n)	MATERNAL AGE (years)	GESTATIONAL AGE (WEEKS)	DURATION INERVATION
M. Samimi (2015)	Iran	Randomized Controlled Trial	Aged 18–40 years old, (16–20 weeks)	vitamin D + calcium	50 000 IU vitamin D3 every 2 weeks + 1000 mg day 1 calcium supplementation	60	<30 and ≥30 years	20 to 32 weeks of gestation.	12 weeks
M. Karamali (2015)	Iran	Randomized Double-blind Placebo-Controlled Clinical Trial	aged 18–40 years old (18– 20 weeks)	vitamin D	50000 IU vitamin D3, 14 days for 12 weeks	60	<30 and ≥30 years	20 to 32 weeks of gestation.	12 weeks
Milad Azami (2015)	Iran	Randomized Controlled Trial	Maternal age >35 years (20 weeks)	Group A : Ferrous Sulfate tablet + Vitamin D Group B : Ferrous Sulfate tablet + vitamin C dan vitamin E	Group A : 800mg calcium, 200mg magnesium, 8mg zinc, and 400 IU Vitamin D3 per day Group B : Ferrous Sulfate (1 tablet/da	Group A (n=30)	Group A (33) Group B (31,73)	Group A (37) Group B (38)	Non Specific

					y) + 250 mg vitamin C + 55 mg vitamin E				
Aisha Mansoor Ali (2018)	Saudi Arabia	study	Include pre-eclampsia (22-23 weeks)	vitamin D3 supplementation 400 IU (Group 1) versus 4000 IU (Group 2)	4000 IU daily dose of vitamin D	179 pregnant woman (group 400IU=81 group 4000IU=83)	< 20 years or > 40 years	Between 6 and 12 weeks of pregnancy.	32 weeks

**Table 2. collection outcome dan metabolic profiles**

First author	Outcome	Metabolik
M. Samimi	Caesarean section : 14% Gestational age : 38.4 weeks Preterm delivery : 2 % Newborn weight : 3300.0 g Newborn length : 49.5 cm Newborn head circumference: 34.5 cm Pre-eclampsia rate : 1% LBW : 0%	Vitamin D : 13.1 ng /mL Calcium : 8.7 mg/dL Insulin : 14.3 IU/mL HOMA-IR : 3.1 HOMA-B : 55.5 Triglycerides: 188.5 mg/dl VLDL-cholesterol : 37.7 mg/dl Total cholesterol : 215.9 mg/dl LDL-cholesterol : 108.9 mg/dl HDL-cholesterol : 69.3 mg/dl Total: HDL cholesterol ratio : 3.1
M.Karamali	Caesarean section : 9% Gestational age : 39.4 weeks Preterm delivery : 0 % Newborn weight : 3313.6g Newborn length : 50.9 cm Newborn head circumference: 34.4 cm Pre-eclampsia rate : 1%	Vitamin D : 34.91 ng /mL Insulin : 12.3 IU/mL HOMA-IR : 2.48 HOMA-B : 49.04 Triglycerides: 205.68 mg/dl VLDL-cholesterol : 41.3 mg/dl

	LBW : 0%	Total cholesterol : 222.47 mgdl LDL-cholesterol : 112.86 mg/dl HDL-cholesterol : 68.28 mg/dl Total: HDL cholesterol ratio : 3.26
Milad Azami	Multimineral-vitamin D during pregnancy can be a low-cost and affordable way to reduce the incidence of pre-eclampsia in women who are at high risk of pre-eclampsia.	Non specific
Aisha Mansoor Ali	Vitamin D supplementation in the deficient group reduces the risk of pre-eclampsia and IUGR in a dose dependant manner.	Non specific

According to (Azami et al., 2017) and (Samimi et al., 2016) who combine Vitamin D with other supplements, results on Vitamin D less effect on reducing the risk of pre-eclampsia but still has a positive effect. However, for Vitamin D given in combination, it has a beneficial effect on reducing the risk of pre-eclampsia and also has a positive impact on the fetus and oxidative stress.

## DISCUSSION

This study was conducted to determine whether there is an effect of Vitamin D on pregnant women with pre-eclampsia. Pre-eclampsia is a multisystem pregnancy disease characterized by complex

hypertension with serious consequences for the mother, fetus, and neonate, burdening up to 8% of pregnancies. Vitamin D deficiency results in a higher risk of pre-eclampsia (Mirzakhani et al., 2016).

Several studies have proven that vitamin D had a significant effect on reducing the risk of pre-eclampsia and it could reduce early birth rates. However, a combination of Vitamin D with other supplements has a nonoptimal effect. However, it can still reduce the risk of pre-eclampsia and reduce the rate of premature birth with oral administration at high doses. It can be concluded that the administration of Vitamin D with normal doses to a high limit can reduce the risk of pre-eclampsia for pregnant women. Low

vitamin D intake can impair ongoing oxidative stress processes in placental tissue and may increase the risk of pre-eclampsia (Ali et al., 2019).

Administration of high doses of Vitamin D with an average of 4000IU with a recommendation of 600IU intake a day, it's given for 12-32 weeks. Women at risk of pre-eclampsia who have Vitamin D deficiency had beneficial effects on insulin metabolism parameters, serum HDL cholesterol, and plasma TAC concentrations, but did not affect FPG, another lipid profile, inflammatory factors,

and other oxidative stress biomarkers (Karamali et al., 2015).

The association between vitamin D deficiency, pre-eclampsia, fetal growth and suggests that vitamin D supplementation may improve pregnancy outcomes and fetal growth problems in the high-risk group. Overall, it appears that multiminerals-vitamin D supplementation in pregnant women at risk of pre-eclampsia reduces the risk of neonatal complications by reducing the incidence of pre-eclampsia (Azami et al., 2017).

## CONCLUSIONS

Based on the results of this study, a high dose of vitamin D has a good effect on reducing the risk of pre-eclampsia in pregnant women with vitamin D deficiency.

Vitamin D can reduce oxidative stress as a factor in pre-eclampsia and stimulate immunity in multiple tissues and promote proper and healthy placental function. This is one of the reasons why vitamin D has a positive relationship with pre-eclampsia.

## REFERENCES

- Ali, A. M., Alobaid, A., Malhis, T. N., & Khattab, A. F. (2019). Effect of vitamin D3 supplementation in pregnancy on risk of pre-eclampsia – Randomized controlled trial. *Clinical Nutrition, 38*(2), 557–563. <https://doi.org/10.1016/j.clnu.2018.02.023>
- Amrein, K., Scherkl, M., Hoffmann, M., Neuwersch-Sommeregger, S., Köstenberger, M., Tmava Berisha, A., Martucci, G., Pilz, S., & Malle, O. (2020). Vitamin D deficiency 2.0: an update on the current status worldwide. *European Journal of Clinical Nutrition, 74*(11), 1498–1513. <https://doi.org/10.1038/s41430-020-0558-y>
- Azami, M., Azadi, T., Sc, M., Farhang, S., Rahmati, S., & Pourtaghi, K. (2017). The effects of multi mineral-vitamin D and vitamins (C+E) supplementation in the prevention of preeclampsia: An RCT. In *Int J Reprod BioMed* (Vol. 15, Issue 5).
- Karamali, M., Beihaghi, E., Mohammadi, A. A., & Asemi, Z. (2015). Effects of high-dose Vitamin D supplementation on metabolic status and pregnancy outcomes in pregnant women at risk for pre-eclampsia. *Hormone and Metabolic Research, 47*(12), 867–872. <https://doi.org/10.1055/s-0035-1548835>



Mirzakhani, H., Litonjua, A. A., McElrath, T. F., O'Connor, G., Lee-Parritz, A., Iverson, R., MacOnes, G., Strunk, R. C., Bacharier, L. B., Zeiger, R., Hollis, B. W., Handy, D. E., Sharma, A., Laranjo, N., Carey, V., Qiu, W., Santolini, M., Liu, S., Chhabra, D., ... Weiss, S. T. (2016). Early pregnancy Vitamin D status and risk of preeclampsia. *Journal of Clinical Investigation*, 126(12), 4702–4715. <https://doi.org/10.1172/JCI89031>

Samimi, M., Kashi, M., Foroozanfard, F.,

Karamali, M., Bahmani, F., Asemi, Z., Hamidian, Y., Talari, H. R., & Esmailzadeh, A. (2016). The effects of vitamin D plus calcium supplementation on metabolic profiles, biomarkers of inflammation, oxidative stress and pregnancy outcomes in pregnant women at risk for pre-eclampsia. *Journal of Human Nutrition and Dietetics*, 29(4), 505–515.

<https://doi.org/10.1111/jhn.12339>



© 2021 by the authors. Submitted for possible open access publication

under the terms and conditions of the Creative Commons Attribution (CC BY SA) license (<https://creativecommons.org/licenses/by-sa/4.0/>).