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Effect of High-Dose Vitamin D on Angiogenesis Markers in High-Risk Pregnant Women

Nunki Febriastuti,[1] Rima Irwinda,[2] Noroyono Wibowo,[2] Damar Prasmusinto,[2] Yudianto B. Saroyo,[2] Yuditiya Purwosunu[2]

[1]Department of Obstetrics and Gynecology, Koja District Hospital, North Jakarta, Indonesia
[2]Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Indonesia-dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Abstract

Preeclampsia is characterized by impaired trophoblast invasion and angiogenesis. Recent evidence suggests that vitamin D supplementation may reduce the risk of preeclampsia by optimizing angiogenesis. This study aimed to evaluate the effect of high-dose vitamin D on angiogenesis markers in the first trimester by evaluating serum maternal placental growth factor (PlGF) and uterine artery pulsality index (UtA-PI) in pregnant women with a high risk for preeclampsia. A single-blind, randomized controlled trial was conducted on 80 pregnant women from April 2021 to April 2022 at Dr. Cipto Mangunkusumo National General Hospital and Koja District Hospital. Pregnant women at 7–11 weeks of gestation were divided into low-risk and high-risk preeclampsia groups. Each group was then randomized into a control group (multi-micronutrient supplementation/MMS) and an intervention group (MMS + vitamin D at 5,000 IU/day). Maternal serum 25(OH)D levels and PlGF levels, as well as Doppler UtA-PI, were measured at baseline and after one month of intervention. All participants had vitamin D deficiency at baseline. After one month, the increase in 25(OH)D level was significantly higher in the low-risk group (12.3±6.3 ng/mL vs 10.5±5.1 ng/, p<0.001). Mean UtA-PI was significantly reduced in both low-risk (-1.1±0.3) and high-risk (-0.43±0.26) intervention groups. PlGF level increasedwas significantly in both intervention groups (low-risk 107.9±32.0 vs. high-risk 70.5±18.3, p<0.001). High-dose vitamin D supplementation (5,000 IU/day) improves angiogenesis in the first trimester, suggesting potential benefits for improving pregnancy outcomes in women at risk for preeclampsia.

Keywords: 25-Hydroxyvitamin D, placental growth factor, preeclampsia, uterine artery

Introduction

Preeclampsia is a major cause of maternal and fetal morbidity and mortality worldwide, affecting approximately 2–10% of all pregnancies.[1] In Indonesia, the incidence of preeclampsia was reported to be 33.03% according to data from the Indonesian Ministry of Health in 2020, making it one of the leading cause of maternal mortality. Data from the Indonesian Ministry of Health (2017) showed that hypertension accounted for 28% of maternal death, followed by eclampsia (24%) and hemorrhage during pregnancy (11%).[2,3] Currently, the only definitive treatment for preeclampsia is delivery of the fetus and placenta, which often result in preterm birth. Therefore, early prediction and prevention of preeclampsia are essential to reduce maternal and neonatal morbidity and mortality.[4]

Preeclampsia is a multifactorial disorder of pregnancy involving impaired trophoblast invasion, abnormal vascular remodeling, oxidative stress and dysregulated maternal immune responses. Inadequate spiral artery remodeling and impaired placental angiogenesis lead to increased vascular resistance, reflected by an imbalance between pro-angiogenic and anti-angiogenic factors. This imbalance includes decreased levels of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), along with increased levels of soluble fms-like tyrosine kinase-1 (sFlt-1), and is associated with an increase uterine artery pulsatility index (UtA-PI).[5]

Currently, low-dose aspirin and calcium supplementation are recommended to prevent preeclampsia in high-risk pregnant women or in those with low calcium intake. Vitamin D

Corresponding Author:
Nunki Febriastuti
Department of Obstetrics and Gynecology, Koja District Hospital, North Jakarta, Indonesia
Email: nunki.febriastuti@gmail.com

has also been suggested to regulate placental function through its effect on trophoblast invasion, angiogenesis, immune modulation, and antioxidant activity. Several studies have reported that vitamin D deficiency is significantly associated with an increased risk of preeclampsia, whereas vitamin D supplementation is associated with a reduced risk.[4–6] In a study conducted by Ali et al. in Saudi Arabia, supplementation with 4,000 IU of vitamin D was associated with a lower risk of preeclampsia compared with 400 IU (1.2% vs 8.6%).[7] Furthermore, a previous research study by Noroyono et al. reported that 99% of pregnant women in the first trimester in Jakarta had serum 25- hydroxyvitamin D [25(OH) D] levels below 30 ng/mL.[8] Another study also reported a lower incidence of preeclampsia among high-risk pregnant women who received high-dose vitamin D_3.[9] Therefore, this study aimed to evaluate the effect of high-dose vitamin D supplementation in first-trimester pregnant women at high risk of preeclampsia in Jakarta by assessing angiogenesis markers, specifically maternal serum PlGF levels and uterine artery pulsatility (UtA-PI).

Methods

This study was a single-blind randomized controlled trial (participants and outcome assessors), approved by the Health Research Ethics Committee of the faculty of Medicine, Universitas Indonesia–dr. Cipto Mangunkusumo Hospital (FKUI-RSCM) (No.KET.325/UN2. F1/ETIK/PPM.00.02.2021). The study was conducted from April 2021 to April 2022 at Cipto Mangunkusumo Hospital and Koja District Hospital, Jakarta. The inclusion criteria were pregnant women at 7–11 weeks ofgestation with a singleton live fetus confirmed by ultrasound examination. Pregnant women with multiple pregnancies, congenital fetal anomalies, or those who had taken high-dose vitamin D supplementation prior to enrollment were excluded. Participants who experienced miscarriage, missed vitamin supplementation for more than three days, or were diagnosed with COVID-19 during the study were considered dropouts.

All eligible pregnant women were informed about the study procedures and provided written informed consent prior to participation. Participants were categorized into low-risk and high-risk factor for preeclampsia groups. Subjects with one high-risk factor or two moderate-risks factors for preeclampsia based on American College of Obstetricians and Gynecologists (ACOG) criteria (Table 1) were classified as high-risk.[10] Each group was subsequently allocated into control and intervention groups using simple randomization. The control group received multiple micronutrient supplementation (MMS), while the intervention group received MMS plus vitamin D supplementation at a dose of 5,000 IU per day for one month.

Sample size calculation was performed using

Table 1 Risk Factors for Preeclampsia

Category	Risk Factors
High Risk	History of preeclampsia, particularly with adverse outcomes
	Multifetal gestation
	Chronic hypertension
	Type 1 or type 2 diabetes mellitus
	Renal disease
	Autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome)
Moderate risk	Nulliparity
	Obesity (BMI > 30 kg/m2)
	Family history of preeclampsia (mother or sister)
	Sociodemographic factor (African American race, low socioeconomic status)
	Maternal age ≥35 years
	Other factors: low birth weight or small for gestational age, previous adverse pregnancy outcome, pregnancy interval > 10 years

the formula for paired numerical comparative analytical studies between two groups, resulting in a total sample size of 80 participants (10 participants in each subgroup).

At baseline, all subjects underwent medical history taking, physical examination, and ultrasound examination to determine gestational age and to measure uterine artery pulsatility index (UtA-PI). Blood samples were also collected to determine baseline serum 25-hydroxyvitamin D_3 [$25(OH)D_3$] levels. The intervention was administered according to coded labels to maintaining blinding. Participants were instructed not to change their physical activity or dietary intake and not to take additional vitamin supplements other than those provided by the researcher. After one month of intervention, subjects underwent repeat ultrasound examination for UtA-PI measurement and blood sampling to assess serum $25(OH)D_3$ and placental growth factor (PlGF) levels.

Serum $25(OH)D_3$ levels were measured using direct competitive chemiluminescence immunoassay (CLIA) method with the LIAISON® 25-OH Vitamin D assay. Maternal serum PlGF levels were measured using an electrochemiluminescence immunoassay (ECLIA) with the Cobas e601/elecsys analyzer (Roche Diagnostics) at the Prodia Research Laboratory, Jakarta. UtA-PI measurements were performed by the researcher using Doppler ultrasound with a Voluson P8 system. The examination involved obtaining a sagittal section of the uterus with identification of the cervix, followed by localization of the uterine arteries at the level of the internal cervical os using color Doppler mapping. Pulsed-wave Doppler was then applied with a 2 mm sampling gate and an insonation angle of less than 30°. After obtaining three consecutive similar waveforms, the pulsatility indices of both the left and right uterine arteries were measured, and the mean value was calculated.

Statistical analyses were perfomed using SPSS version 26. Normality of the data distribution was assessed using Saphiro-Wilk test. Differences between groups were analyzedusing independent t-test. A p-value <0.05 was considered statistically significant.

Results

Among 92 pregnant women screened at 7–11 weeks of gestational, 80 completed the trial and were included in the final analysis. Participants were categorized into low and high-risk preeclampsia groups and subsequently randomized into control and intervention groups, with 20 subjects in each group. Compliance with vitamin supplementation was monitored weekly through telephone interviews. Figure 1 illustrates the enrollment, allocation, and follow-up of the participants throughout the study.

Characteristics of subjects are shown in Table 1. There were no significant difference in age or body mass index (BMI) between the low and high-risk group. However, within the

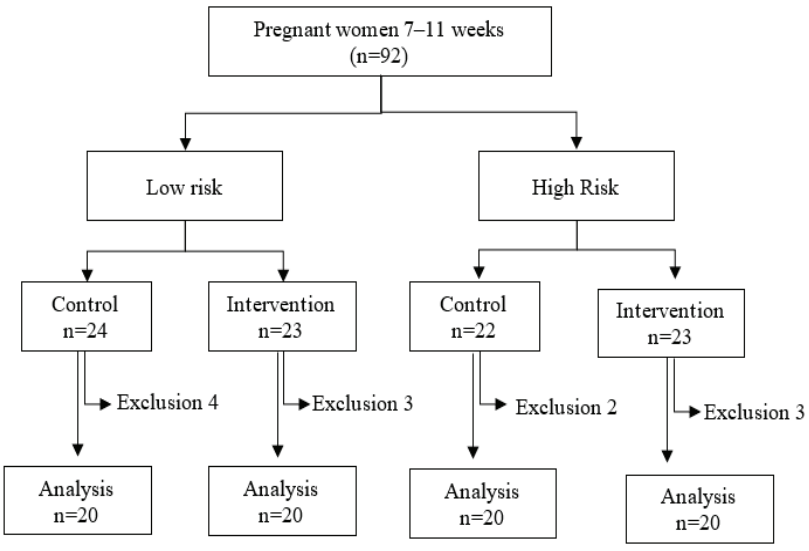

Figure 1 Research Flow Diagram

Table 1 Characteristics of Subjects In Low and High-Risk Groups

Variable	Low-risk Group		High-risk Group	
	Control	Intervention	Control	Intervention
Age (years)	29.0±3.8	30.50(4.00)	30.7±5.9	30.3±5.2
Body weight (kg)	61±10.8	61.0±10.1	81.5±15.6	71.9±15.2
Height (m)	1.56(0.30)	1.6±0.05	1.6±0.05	1.55±0.03
BMI (kg/m^2)	24.99(4.64)	25.0±4.1	33.0±6.0	29.7±5.7
Blood Pressure (mmHg)				
Systolic	110.0±10.6	112.6±10.8	122.9±12.3	121.1±15.2
Diastolic	67.3±6.4	75.3±8.1*	77.75±8.64	79.6±10.8
MAP	81.5±7.1	87.7±8.1*	92.8±8.7	94.5±11.8
Gestational age (weeks)	8.6±0.9	8.4±1.3	8.3±1.0	9.5±1.6**

Unpaired T-test; * p<0.05 between control and intervention groups in the low-risk group; ** p<0.05 between control and intervention groups in the high-risk group

low-risk group, diastolic blood pressure and mean arterial pressure (MAP) were significantly higher in the intervention group compared with the control group (p<0.05). In the high-risk group, gestational age was significantly higher in the intervention group than in the control group (p<0.05).

Changes in uterine artery pulsatility index (UtA-PI), serum 25-hydroxyvitamin D_3 [25(OH) D_3], and placental growth factor (PlGF) levels are presented in Table 2. A significant increase in serum 25(OH)D_3 levels was observed in the intervention groups in both the low-risk and high-risk groups, with a greater increase in the low-risk group. PlGF levels were also significantly higher in the intervention groups compared with the control groups.

The decrease in UtA-PI was greatest in the low-risk intervention group. In contrast, no significant difference in UtA-PI reduction was observed between the control and intervention groups in the high-risk group.

Discussion

Higher body mass index (BMI) was observed in the high-risk group, which is a recognizedrisk factors for preeclampsia. A meta-analysis reported that the risk of preeclampsia increases

Table 2 Uterine Artery Pulsatility Index, Maternal Serum 25(OH)D_3, and PlGF Levels in Low- and High-Risk Groups

Variable	Low-risk Group			High-risk Group			p#
	Control	Intervention	p*	Control	Intervention	p*	
Mean UtA-PI							
First visit	2.4±0.3	2.5±0.5	0.277	2.6±0.4	2.3±0.4	0.006	0.636
Second visit	1.8±0.3	1.4±0.4	0.001	2.0±0.4	1.9±0.3	0.216	0.191
Δ (change)	-06±0.4	-1.1±0.3	<0.001	-0.6±0.3	-0.4±0.3	0.031	<0.001
25(OH)D_3							
First visit	13.3±5.8	15.7±6.01	0.209	11.2±3.8	14.8±5.8	0.029	0.082
Second visit	14.1±5.9	28.0±8.3	<0.001	9.9±3.4	25.2±4.2	<0.001	0.001
Δ (change)	0.8±1.3	12.3±6.2	<0.001	-1.35±1.0	10.5±5.1	<0.001	<0.001
PlGF level	84.3±10.0	107.8±32.0	0.005	37.6±9.7	70.5±18.32	<0.001	<0.001

* Unpaired T-test between control and intervention groups; # Unpaired T-test between intervention low-risk and high-risk groups

with increasing BMI, indicating that BMI can be considered an important risk factor for the development of preeclampsia.[11]

All participants in this study had vitamin D deficiency at baseline. This finding is consistent withprevious research reporting that 99.6% of pregnant women in the first trimester in Jakarta have vitamin D deficiency.[8] A meta-analysis including six studies involving 830 Indonesian pregnant women reported prevalence rates of vitamin D insufficiency, deficiency, and hypovitaminosis D of 25%, 63% and 78%, respectively. Despite Indonesia being a tropical country with abudant sunlight throughout the year, lifestyle factors such as wearing heavy clothing (e.g., hijab), frequent use of sunscreen or umbrellas, limited sun exposure, and air pollution may contribute to the high prevalence of vitamin D deficiency among Indonesian pregnant women.[12]

Currently, routine vitamin D supplementation during pregnancy is not recommend by the Indonesian Ministry of Health. According to the Institute of Medicine, the recommended dietary allowance of vitamin D during pregnancy is 600 IU/day with an upper intake limit of 4,000 IU/day. Meanwhile, the Endocrine Society Clinical Practice Guideline recommends vitamin D_3 supplementation of 50,000 IU weekly for eight weeks in adult with vitamin D deficiency. Syafitri et al. evaluate the effects of different vitamin D_3 supplementation regimens (5,000 IU daily vs 50,000 IU weekly) on maternal vitamin D metabolites and reported that both regimens were equally effective and safe in pregnant women with vitamin D deficiency or insufficiency.[13] In the present study, supplementation with vitamin D 5,000 IU/day for one month significantly increased serum 25(OH)D_3 levels in both low-risk and high-risk groups.

The increase in serum 25(OH)D levels was lower in the high-risk group compared with the low-risk group. This may be explained by the higher BMI observed in the high-risk group. A randomized double-blind clinical trial conducted in Northern Ireland reported that the increase in serum 25(OH)D_3 levels after vitamin D supplementation was lower in individuals witha group of patients with normal BMI and BMI above 25 kg/m^2, of in patients with BMI above 25 kg/m^2 compared with normal BMI.[14]

Consistent with previous studies, the present study showed UtA-PI decreased with advancing gestational age, likely reflecting reduced uterine vascular resistance following trophoblastic invasion of the spiral arteries.[15] UtA-PI values were higher in the high-risk group than in the low-risk group. In normal pregnancy, the uteroplacental circulation forms a low-resistance vascular bed that supports optimal placental development and maintenance of pregnancy. Increased uterine artery resistance, reflected by elevated UtA-PI, is associated with inadequate spiral artery remodeling and may lead to pregnancy complications such as preeclampsia and fetal growth restriction.[16,17]

Vitamin D act as an immunomodulator and regulator of angiogenesis, influencing placentation process including trophoblast differentiation and extravillous trophoblast invasion into the decidua and myometrium, which are critical for spiral artery remodeling.[18] In this study, vitamin D supplementation at dose 5,000 IU/day resulted in a significant decrease in UtA-PI both low-risk and high-risk groups, with the greatest reduction observed in the low-risk intervention group. Notably, none of the participants in the high-risk intervention group had UtA-PI values above the 95th percentile, whereas two participants (10%) in the high-risk control group had UtA-PI values above this threshold.

Higher PlGF levels were observed in both low-risk and high-risk intervention groups. Previous human studies have demonstrated an association between vitamin D insufficiency and endothelial dysfunction, suggesting that vitamin D plays an important role in regulating vascular angiogenesis. Vitamin D has been shown to stimulate the production of vascular endothelial growth factor (VEGF) and placental growth factor (PIGF), both of which are pro-angiogenic factors involved in early placental vascularization.[19] These findings are consistent with a Norwegian study reporting that women who received vitamin D supplementation before and during pregnancy had a 29% lower risk of developing preeclampsia compared with those who did not received supplementation.[20] In a cohort study by Xu et al., vitamin D supplementation administered during early gestation was associated with restoration of angiogenic balance and a significant increase in PlGF levels.[21]

To current knowledge, this is the first study to evaluate the effect of vitamin D supplementation at a dose of 5,000 IU/day on both uterine artery pulsatility index (UtA-PI) and maternal serum placental growth factor (PlGF) levels in first-trimester pregnant women at high risk of preeclampsia. However, several limitations should be acknowledged. The single-blind

design may introduce potential bias, and other biomarkers that may influence the biological effects of vitamin D were not assessed. In addition, participants were not followed until delivery to evaluate pregnancy outcomes.

In conclusion, supplementation with vitamin D at a dose of 5,000 IU/day was associated with significantly higher serum 25(OH)D and PlGF levels, along with lower UtA-PI values, suggesting a potential benefit in improving angiogenesis during early pregnancy and possibly reducing the risk of preeclampsia.

References

1. Khan B, Allah Yar R, Khakwani AK, Karim S, Arslan Ali H. Preeclampsia incidence and its maternal and neonatal outcomes with associated risk factors. Cureus. 2022;14(11):e31143. doi:10.7759/cureus.31143
2. Profil Kesehatan Indonesia tahun, 2019. Indonesia: Kementerian Kesehatan RI; 2020.
3. Budayasa AR, Afiatin, Kuncoro AS, Juli C, Harmeiwaty E, Bachnas MA, et al. Panduan penatalaksanaan hipertensi pada periode peripartum. Jakarta: Indonesian Society of Hypertension (InaSH); 2025.
4. Chen WY, Sun SF. Clinical efficacy of low-dose aspirin combined with calcium in preventing preeclampsia: a systematic review and meta-analysis. Medicine (Baltimore). 2023;102(34):e34620. doi:10.1097/MD.0000000000034620
5. Zheng S, Dong S, Shen H, Xu P, Shu C. Role of vitamin D in the pathogenesis of early-onset preeclampsia: a narrative review. Front Nutr. 2025;12:1598691.
6. AlSubai A, Baqai MH, Agha H, Shankarlal N, Javaid SS, Jesrani EK, et al. Vitamin D and preeclampsia: A systematic review and meta-analysis. SAGE Open Med. 2023;11:20503121231212093. doi:10.3389/fnut.2025.1598691
7. Ali AM, Alobaid A, Malhis TN, Khattab AF. Effect of vitamin D3 supplementation in pregnancy on the risk of pre-eclampsia -randomized controlled trials. Clin Nutr. 2019;38(2):557–63. doi:10.1016/j.clnu.2018.02.023
8. Wibowo N, Bardosono S, Irwinda R, Syafitri I, Putri AS, Prameswari N. Assessment of the nutrient intake and micronutrient status in the first trimester of pregnant women in Jakarta. Med J Indones. 2017;26(2):109–15. doi:10.13181/mji.v26i2.1617
9. Xiaomang J, Yanling W. Effect of vitamin D3 supplementation during pregnancy on high risk factors - a randomized controlled trial. J Perinat Med. 2020;49(4):480–4. doi:10.1515/jpm-2020-0318 doi:10.1515/jpm-2020-0318.
10. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol. 2019;133(1):e1-e25.
11. Motedayen M, Rafiei M, Rezaei Tavirani M, Sayehmiri K, Dousti M. The relationship between body mass index and preeclampsia: A systematic review and meta-analysis. Int J Reprod Biomed. 201;17(7):463–72. doi:10.18502/ijrm.v17i7.4857
12. Octavius GS, Daleni VA, Angeline G, Virliani C. A systematic review and meta-analysis of prevalence of vitamin D deficiency among Indonesian pregnant women: a public health emergency. AJOG Glob Rep. 2023;3(2):100189. doi:10.1016/j.xagr.2023.100189
13. Syafitri I, Irwinda R, Saroyo YB, Purwosunu Y, Wibowo N. Maternal concentrations of vitamin D metabolites in response to high-dose oral vitamin D during first trimester pregnancy: a randomized controlled trial. BMC Nutr. 2025;11(1):117. doi:10.1186/s40795-025-01104-3
14. Alhomaid RM, Mulhern Ms, Strain JJ, Eamon L, Healy M, Parker MJ, McCann MT. Maternal obesity and baseline vitamin D insufficiency alter the response to vitamin D supplementation: a double-blind, randomized trial in pregnant women. Am J Clin Nutr. 2021;114:1208–18. doi:10.1093/ajcn/nqab112
15. Cavoretto PI, Salmeri N, Candiani M, Farina A. Reference ranges of uterine artery pulsatility index from first to third trimester based on serial Doppler measurements: longitudinal cohort study. Ultrasound Obstet Gynecol. 2023;61(4):474–80. doi:10.1002/uog.26092.
16. Wang S, Dong H. Non-linear dose-response relationship between uterine artery pulsatility index and risk of preeclampsia in early pregnancy: A secondary analysis based on a nested cohort study. PLoS One. 2025;20(1):e0317625. doi:10.1371/journal.pone.0317625
17. Pennington KA, Beffa LB, Schust DJ. Early placental developmnet and disorders. In: Farquharson RG, Stephenson MD, eds. Early Pregnany. Cambridge: Cambridge University

Press; 2017. p. 43–53
18. Ganguly A, Tamblyn JA, Finn-Sell S, Chan S-Y, Westwood M, Gupta J, et al. Vitamin D, the placenta and early pregnancy: effects on trophoblast function. J Endocrinol. 2018;236(2):R93–R103. doi:10.1530/JOE-17-0491
19. Schulz EV, Cruze L, Wei W, Gehris J, Wagner CL. Maternal vitamin D sufficiency and reduced placental gene expression in angiogenic biomarkers related to comorbidities of pregnancy. J Steroid Biochem Mol Biol. 2017;173:273–9. doi:10.1016/j.jsbmb.2017.02.003
20. Behjat Sasan S, Zandvakili F, Soufizadeh N, Baybordi E. The effects of vitamin D supplement on prevention of recurrence of preeclampsia in pregnant women with a history of preeclampsia. Obstet Gynecol Int. 2017;2017:8249264. doi:10.1155/2017/8249264
21. Xu J JX, Gu Y, Lewis DF, Gu X, Wang Y. Vitamin D reduces oxidative stress-induced procaspase-3/ROCK1 activation and MP release by placental trophoblasts. J Clin Endocrinol Metab. 2017;102:2100–10. doi:10.1210/jc.2016-3753