

## Vitamin D Deficiency in Pregnancy: A Systematic Review

Fannysha Arrahma<sup>1</sup>, Iche Andriyani Liberty<sup>2\*</sup>

<sup>1</sup>Medical Doctor Professional Study Program, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia

<sup>2</sup>Department of Public Health and Community Medicine, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia

E-mail: ichealiberty@yahoo.com

### Abstract

Vitamin D deficiency (VDD) is a common problem in reproductive-aged women and has become a major public health problem worldwide. Adverse health outcomes such as preeclampsia, low birthweight, neonatal hypocalcemia, poor postnatal growth, bone fragility, and increased incidence of autoimmune diseases have been linked to low vitamin D levels during pregnancy and infancy. A systematic literature search was performed on September 6th – 21st, 2022 using respected database. The identified articles were screened using the chosen eligibility criteria. Literature selection was performed with rest time restriction from January 1, 2017, and September 22, 2022 and restricted to only published in English articles. Three papers were evaluated in full-text after duplicates were removed. Tammo et al, Mansur et al and Moralez et al were the three studies that remained following full-text screening utilizing eligibility criteria and quality assessment showing a significant proof regarding this review. Vitamin D deficiency had wide variety of effects in pregnancy as it may increased risk of multisystem disorders in pregnancy such as preeclampsia, low birth weight in neonates, insulin resistance, gestational diabetes mellitus (GDM), and a higher risk of primary cesarean delivery. Optimal level of 30 ng/mL or more before conception and throughout the entire pregnancy with different dosages available, avoiding levels below 20 ng/ml.

Keywords: vitamin D, deficiency, pregnancy

### 1. Introduction

Vitamin D deficiency (VDD) is a common problem in reproductive-aged women and has become a major public health problem worldwide. The effect of VDD in pregnancy has been associated with several adverse pregnancy outcomes.<sup>1</sup>

Vitamin D itself is an essential fat soluble vitamin and a key modulator of calcium metabolism in children and adults. Vitamin D and parathyroid hormone are important in calcium homeostasis and bone mineralization.<sup>2</sup> Because calcium demands increase in the third trimester of pregnancy, vitamin D status becomes crucial for maternal health, fetal skeletal growth, and optimal maternal and fetal outcomes. Vitamin D deficiency is common in pregnant women (5–50%) and in breastfed infants (10–56%), despite the widespread use of prenatal

vitamins, because these are inadequate to maintain normal vitamin D levels ( $\geq 32$  ng/mL). Adverse health outcomes such as preeclampsia, low birthweight, neonatal hypocalcemia, poor postnatal growth, bone fragility, and increased incidence of autoimmune diseases have been linked to low vitamin D levels during pregnancy and infancy.<sup>3-5</sup>

Indonesia is a tropical country with abundant sun exposure, as it lies within the equatorial zone. However, low vitamin D status is still found in such countries Several studies on vitamin D status in pregnant women and women of childbearing age have been conducted and have shown that an average of more than 95% of individuals have low vitamin D status.<sup>6</sup> Personal lifestyle and cultural factors are important determinants

for vitamin availability because of their influence on sun exposure and dietary intake.<sup>7</sup>

The main source of vitamin D is obtained by direct synthesis from sunlight to the skin and stimulation of pre-vitamin D<sub>3</sub> development. Moreover, intake from diet and supplements will be synthesised as vitamin D<sub>2</sub>. However, dietary intake only provides 10% of vitamin D requirements as very few foods contain a high amount of vitamin D, so vitamin D supplements could be considered as a way of boosting such requirements. When vitamin D deficiency is identified during pregnancy, most experts agree that 1,000–2,000 international units per day of vitamin D is safe. Higher dose regimens used for treatment of vitamin D deficiency have not been studied during pregnancy.<sup>8-9</sup> In this study, we conducted a systematic review about newest findings of vitamin D deficiency in pregnancy.

## 2. Methods

### 2.1. Protocol and Registration

To research association between vitamin D deficiency and pregnancy, we used a comprehensive and up-to-date literature database. This systematic review follows the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) criteria.

### 2.2. Eligibility Criteria

This review includes Prospective and retrospective human studies over the last ten years on vitamin D deficiency and pregnancy that were found in a credible literature database. As a result, articles published prior to 2017 were discarded from this review. Furthermore, all of the following criteria have to be met by the studies: 1) the article must be accessible; 2) both full text and abstract must be available; 3) the article must be written in English; and 4) the article must be published between January 1, 2017, and September 22, 2022.

### 2.3. Search Strategy

On September 6th – 21st, 2022, a systematic literature search was conducted utilizing three databases: Clinical Key, Cochrane, and PubMed using the keywords (“Vitamin D”) AND (“Deficiency”) AND (“Pregnancy”), as well as manual handsearching using the keywords “Vitamin D” AND "Deficiency" AND “Pregnancy”.

**Table 1. Search Strategies used in electronic databases**

Databases	Search Query	Hits
Clinical Key	(“Vitamin D”) AND (“Deficiency”) AND (“Pregnancy”)	165
Cochrane	(“Vitamin D”) AND (“Deficiency”) AND (“Pregnancy”)	35
PubMed	(“Vitamin D”) AND (“Deficiency”) AND (“Pregnancy”)	133
Handsearching	“Vitamin D” AND "Deficiency" AND “Pregnancy”	7

### 2.4. Data Collection

The title, author, citation of publication, year of publication, study design, and study variable were all collected by the author from each study. Each reference was checked for possible full-text review, and each full-text publication was checked for inclusion.

### 2.5. Quality Assessment and Data Synthesis

Authors independently assessed certain article titles and abstracts to find potentially eligible studies and read full-text articles to determine final inclusions. Duplicates and unavailable studies were excluded.

## 3. Results

### 3.1. Study Selection

A literature search using the keywords indicated in Table 1 resulted in numerous researches. Following title and abstract screening, 10 articles were found out of 380 total. Seven papers were evaluated in full-text after duplicates were removed. Tammo et al<sup>10</sup>, Mansur et al<sup>11</sup> and Morales et al<sup>12</sup> were the three studies that remained following full-text screening utilizing eligibility criteria and

quality assessment. The procedures taken to select research that met the inclusion criteria

are summarized in the flow diagram (Figure 1).

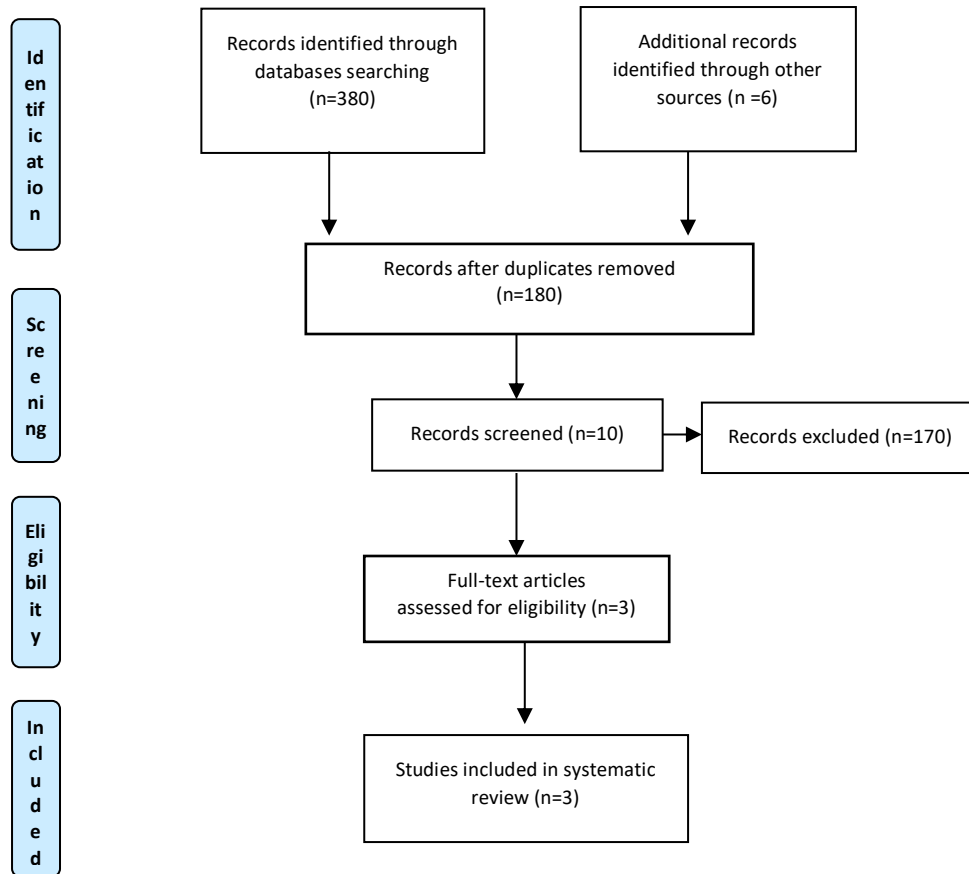


Figure 1. PRISMA flowchart of study selection

Table 2. Characteristics of included studies

Authors (Year)	Study Design	Country	Sample Size	Age of Participant	Findings
Tammo et al <sup>10</sup>	Case control study	Turkey	42 preeclamptic mothers and 49 healthy mothers	NA	There is consistent evidence of an association between low vitamin D concentrations and adverse preeclampsia outcomes. Since vitamin D deficiency is more common in preeclamptic mothers and their infants, higher-dose vitamin D supplementation than routine may be recommended to the patients.
Mansur et al <sup>11</sup>	Literature review	Switzerland	NA	NA	Reaching an optimal level of 30 ng/mL or more before conception and throughout the entire pregnancy with different dosages available, avoiding levels below 20 ng/mL. For the non-classical actions of Vitamin D, values greater than 40 ng/mL were shown to prevent infectious diseases, predominantly respiratory, and effects on autoimmune diseases, with which the intervention would favor prevention.
Moralles et al <sup>12</sup>	Systematic review	Switzerland	14 out of 215 articles	NA	Appropriate levels of vitamin D during pregnancy are associated with less mobility during pregnancy. Supplementary vitamin D for pregnant women is important for reducing the risk of gestational diabetes, hypertension, preeclampsia, early labor, and other complications.

Notes:

NA = Not Available

### **3.2. Study Characteristic**

Two studies were performed in Switzerland, and the other remaining was performed in Turkey. An updated systematic review, case control, and literature review study are included among the papers. Table 2 highlights the three research characteristics utilized to investigate newest findings about vitamin D deficiency in pregnancy.

### **4. Discussion**

Vitamin D is a fat-soluble vitamin produced in the body through the interaction of sunlight with 7-dehydrocholesterol, and it is essential to maintain human health. There are two main isoforms of vitamin D, namely, D3 (cholecalciferol) and D2 (ergocalciferol). Vitamin D3 is derived from ultraviolet-B and is found in foods such as fatty fish, cod liver oil, and egg yolk. Vitamin D2 is derived from the intake of fungal sources such as mushrooms and yeast. Vitamin D deficiency may lead to softening of bones, osteomalacia, and rickets as it plays an important role in bone and calcium (mineral) homeostasis.<sup>13-16</sup> Vitamin D deficiency is a common health problem worldwide. It has been reported that 30%–50% of the population in the United States, Canada, Europe, Australia, New Zealand, and Asia are vitamin D deficient.<sup>17</sup> Tammo et al<sup>10</sup> has confirmed that there is consistent evidence of an association between low vitamin D concentrations and adverse preeclampsia outcomes. Since vitamin D deficiency is more common in preeclamptic mothers and their infants, higher-dose vitamin D supplementation than routine may be recommended to the patients.

As if preeclampsia is a multisystem disease during pregnancy, characterized by the new onset of gestational hypertension and proteinuria. It occurs in around 3–8% of all pregnancies and is associated with increased maternal and fetal morbidity and mortality. Maternal preeclampsia is also associated with

a higher incidence of cardiovascular and kidney disease in the later life of the child.<sup>18</sup>

Vitamin D deficiency had wide variety of effects on pregnancy and still on study. Therefore, it is likely that Vit D has a role in improving endothelial repair and angiogenesis and controlling blood pressure in preeclampsia.<sup>19</sup> Furthermore, the immunomodulatory properties of VitD may also reduce the risk of preeclampsia development.<sup>20</sup> A study by Hu et al<sup>21</sup> stated that Vit D insufficiency (20–30 ng/ml) or deficiency (<20 ng/ml) was associated with an increased risk of preeclampsia. Mansur et al<sup>11</sup> also has come to similar conclusion that reaching an optimal level of 30 ng/mL or more before conception and throughout the entire pregnancy with different dosages available, avoiding levels below 20 ng/mL. For the non-classical actions of Vitamin D, values greater than 40 ng/mL were shown to prevent infectious diseases, predominantly respiratory, and effects on autoimmune diseases, with which the intervention would favor prevention.

Study by Li et al<sup>21</sup> stated that a low vitamin D level is a risk factor for PPH. Low vitamin D also related to high risk of low hemoglobin before delivery. Other study also said that low vitamin D levels during pregnancy lead to an increased rate of low birth weight in neonates, insulin resistance, gestational diabetes mellitus (GDM), and a higher risk of primary cesarean delivery. Therefore, it is strongly suggested that all women should be advised to take vitamin D supplements during pregnancy. Similar with results from Morales et al<sup>12</sup>, appropriate levels of vitamin D during pregnancy are associated with less mobility during pregnancy. Supplementary vitamin D for pregnant women is important for reducing the risk of gestational diabetes, hypertension, preeclampsia, early labor, and other complications.

## 5. Conclusion

From this study, we found that vitamin D deficiency had wide variety of effects in pregnancy as it may increased risk of multisystem disorders in pregnancy such as preeclampsia, low birth weight in neonates, insulin resistance, gestational diabetes mellitus (GDM), and a higher risk of primary cesarean delivery. Optimal level of 30 ng/mL or more before conception and throughout the entire pregnancy with different dosages available, avoiding levels below 20 ng/ml. Further study of newest vitamin D deficiency problems in pregnancy and adverse effect in vitamin D supplementation during pregnancy may be needed to support our evidence found in this study and to be beneficial for best practice .

## References

1. Aji AS, Erwinda E, Yusrawati Y, Malik SG, Lipoeto NI. Vitamin D deficiency status and its related risk factors during early pregnancy: a cross-sectional study of pregnant Minangkabau women, Indonesia. *BMC Pregnancy Childbirth*. 2019 May 22;19(1):183.
2. Triunfo S, Lanzzone A. Potential impact of maternal vitamin D status on obstetric well-being. *J Endocrinol Investig*. 2018;39:37–44.
3. Khalessi N, Kalani M, Araghi M, Farahani Z. The relationship between maternal Vitamin D deficiency and low birth weight neonates. *J Family Reprod Health*. 2017;9:113-7.
4. Mulligan ML, Felton SK, Riek AE, Bernal-Mizrachi C. Implications of vitamin D deficiency in pregnancy and lactation. *Am J Obstet Gynecol*. 2017 May;202(5):429.e1-9.
5. Bodnar LM, Simhan HN, Catov JM, Roberts JM, Platt RW, Diesel JC, et al. Maternal vitamin D status and the risk of mild and severe preeclampsia. *Epidemiology*. 2017;25:207-14.
6. 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 Indonesia*. 2017;26:109-15.
7. Aji AS, Desmawati D, Yerizel E, Lipoeto NI. The association between lifestyle and maternal vitamin D levels during pregnancy in West Sumatra. *Asia Pac J Clin Nutr*. 2018;27:1286-93.
8. ACOG. Vitamin D: Screening and Supplementation During Pregnancy Committee Opinion 495. 2021.
9. Chicote CC, Lorenzo FG, Comité de Comunicación de la Sociedad Española de Bioquímica Clínica y Patología Molecular . *Vitamina D: una perspectiva actual*. Barcelona: Comité de Comunicación de la Sociedad Española de Bioquímica Clínica y Patología Molecular; 2018.
10. Tammo Ö, Yıldız S. Vitamin D Deficiency and Its Clinical Results in Preeclamptic Mothers and Their Babies. *Cureus*. 2022;14(3): e23519.
11. Mansur, J.L.; Oliveri, B.; Giacoia, E.; Fusaro, D.; Costanzo, P.R. Vitamin D: Before, during and after Pregnancy: Effect on Neonates and Children. *Nutrients*. 2022;14:1900.
12. Morales-Suárez-Varela, M.M.; Uçar, N.; Peraita-Costa, I.; Huertas, M.F.; Soriano, J.M.; Llopis-Morales, A.; Grant, W.B. Vitamin D-Related Risk Factors for Maternal Morbidity during Pregnancy: A Systematic Review. *Nutrients*. 2022;14:3166.
13. Dovnik A, Mujezinovic F. The Association of Vitamin D Levels With Common Pregnancy Complications. *Nutrients*. 2018;10(7):867.
14. Van der Pligt P, Willcox J, Szymlek-Gay

- EA, Murray E, Worsley A, Daly RM. Associations of Maternal Vitamin D Deficiency With Pregnancy and Neonatal Complications in Developing Countries: A Systematic Review. *Nutrients*. 2018;10(5):640.
15. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. *Physiol Rev*. 2016;96(1):365–408.
16. Bischoff-Ferrari HA, Bhasin S, Manson JE. Preventing Fractures and Falls: A Limited Role for Calcium and Vitamin D Supplements? *JAMA*. 2018;319(15):1552–3.
17. Li W-J, Chen K-H, Huang L-W, Tsai Y-L and Seow K-M (2022) Low Maternal Serum 25-Hydroxyvitamin D Concentration Is Associated With Postpartum Hemorrhage: A Retrospective Observational Study. *Front. Endocrinol*. 13:816480.
18. Macedo, T.C.C.; Montagna, E.; Trevisan, C.M.; Zaia, V.; de Oliveira, R.; Barbosa, C.P.; Laganà, A.S.; Bianco, B. Prevalence of preeclampsia and eclampsia in adolescent pregnancy: A systematic review and meta-analysis of 291,247 adolescents worldwide since 1969. *Eur. J. Obstet. Gynecol. Reprod. Biol*. 2020;248:177–86.
19. 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;8249264.
20. Poniedziałek-Czajkowska, E.; Mierzyński, R. Could Vitamin D Be Effective in Prevention of Preeclampsia? *Nutrients*. 2021;13:3854.
21. Hu, K.-L.; Zhang, C.-X.; Chen, P.; Zhang, D.; Hunt, S. Vitamin D Levels in Early and Middle Pregnancy and Preeclampsia, a Systematic Review and MetaAnalysis. *Nutrients*. 2022;14:999.