Systematic Review: The Benefit of Vitamin D Supplementation During Pregnancy

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Abstract

World Health Organization (WHO) states vitamin D deficiency in pregnant women is still high and recognized as a global problem. Vitamin D supplementation can support increasing vitamin D status for pregnant women and babies. This study aims to know the importance of vitamin D during pregnancy and its benefits for pregnant women and their babies. A systematic review of Randomized Controlled Trials (RCT) used PubMed, Science Direct, and Springer Link databases. The determination flow article used the PRISMA diagram. The total number of articles reviewed is four articles. The result has obtained that vitamin D has several benefits if its needs are sufficient during pregnancy, such as reducing the risk of recurrent asthma/wheezing in newborns from mothers with or without asthma, and beneficial in pregnancy with diabetes mellitus. However, the benefits of vitamin D are not proven to change blood pressure at the beginning and middle of pregnancy. Researchers still find inconsistency about the effect of vitamin D on pregnant women if it has compared the results of this article review with another similar research.

Keywords: Vitamin D; pregnancy; maternal health, child health, dietary intake

1. Introduction

Vitamin D deficiency is a health problem that affects more than one billion children and adults worldwide (Holick, 2017). The consequence of vitamin D deficiency during pregnancy cannot consider petty. Vitamin D has a crucial role as an immunomodulator, but it is not a calcium regulator like the unpregnant women. This function is always maintained during pregnancy when the body experiences physiological changes (Hollis and Wagner, 2017).

World Health Organization (WHO) states vitamin D deficiency in pregnant women is still high and recognized as a global problem (Saraf et al. 2016). Vitamin D supplementation has believed to improve maternal and infant vitamin D status. It can assess from the enhancement of 25-hydroxyvitamin D 25(OH)D circulation (Kiely, Wagner and Roth, 2020). However, vitamin D dose recommendations for pregnant women still lack Dietary Reference Value (DRV). Vitamin D deficiency in pregnant women is a common problem when the increasing fetus needs are related to vitamin D intake insufficient and lack of sun exposure. Suspected vitamin D deficiency is related to various pregnancy complications and suboptimal pregnancy outcomes such as preeclampsia, gestational diabetes, premature birth, low birth weight, and even backwardness development nerves in children (Palacios et al., 2016).

Vitamin D can provide an effect on pregnancy and the pseudo-glandular stage in 5-17 weeks of gestation (Kho et al., 2013). Vitamin D status in the blood passes through the cord depending on prenatal vitamin D

status. Moreover, the adequacy of vitamin D during the prenatal period can decrease the risk of asthma at the beginning of a baby's life. Research states that vitamin D administration reduces asthma in babies who birth from mothers with a high risk of asthma [8].

The effectiveness of vitamin D intake needs knowledge about the connection dose-response between 25(OH)D and vitamin D intake, also consideration of safety parameters such as calcium serum (Levy et al., 2021). No result yet or conclusive evidence explaining the benefit, direct prevention of vitamin D for pregnancy outcome, and 25 (OH)D doses still become the primary benchmark to determine the supplementation dose of vitamin D during pregnancy (Kiely, Wagner and Roth, 2020). Based on the description above important for knowing the importance of vitamin D during pregnancy and its benefits for both pregnant women and their baby.

2. Methods

2.1 Search Strategy

In this study literature, the researcher used PubMed, Science Direct, and Springer Link databases. Search literature using the keywords "vitamin D supplementation" and "pregnancy". The researcher only took open-access articles with a Randomized Controlled Trials (RCT) design in 2021, used either Indonesian or English and used pregnant women as the research subject. Moreover, the researcher will exclude articles that do not relate to the benefit or effect of vitamin D intake. The selection process article is based on the PRISMA flow diagram and assessed with a checklist sheet from the Critical Appraisal Skills Program (CASP).

2.2 Screening and Eligibility

The screening process used keywords and inclusion criteria in each database. Next, researchers used the Mendeley application for the duplicate removal process. In the next step, articles will select based on title and abstract suitability through discussion between researchers. The full article was ensured eligible with inclusion criteria, then conducted for article quality assessment.

2.3 Data Extraction

Selected articles were read in full-text mode and conducted for the summary process. It has identified the author, country setting of the study, aims, methodology, and result related to benefit or impact for pregnancy and offspring. Researchers also pay attention to the difference in vitamin D dose used in each study. The discussion between researchers was conducted to make sure the articles have already representative of the research topic.

2.4 Synthesis of Results

The synthesis process in this study used the descriptive method. It is more suitable because the study aims to know the benefit of vitamin D during pregnancy for pregnant women and their babies.

3. Results

Each step of literature searching has shown through the flow diagram below (Fig 1). The final result of the articles has four articles for review. Moreover, the article details have explained in the article extraction table (table 1).

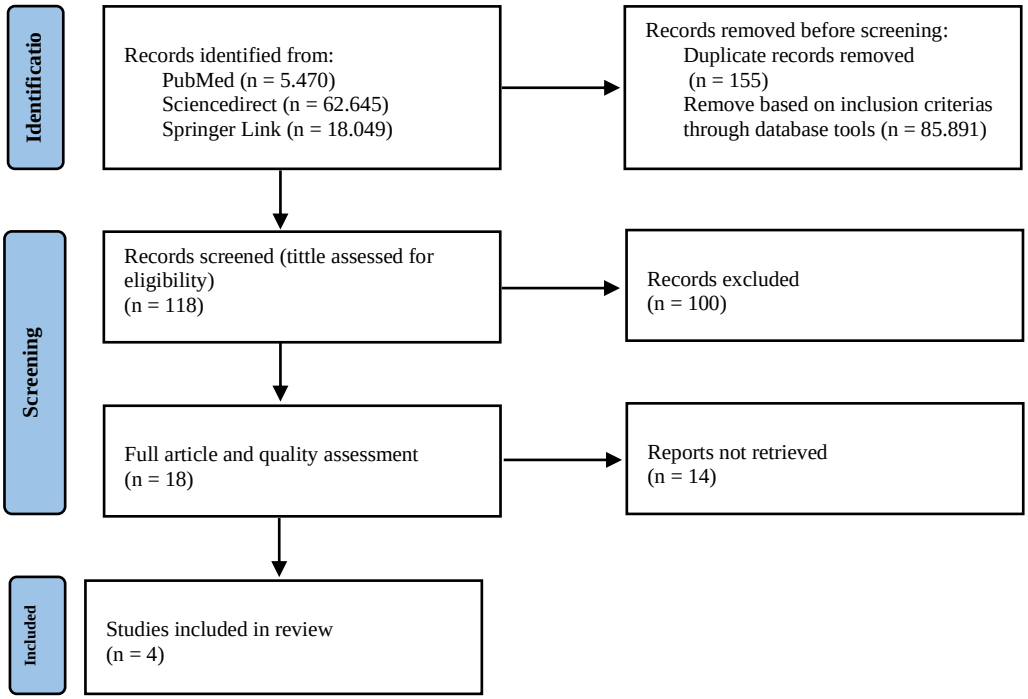

Fig. 1. Literature Searching in PRISMA Flow Diagram

Table 1. Articles Extraction

Article	Country	Purpose	Methods	Results
Huang et al.	China	Knowing the effect of vitamin D and omega-3 against the metabolism of blood glucose and lipids in DMG women	Involved 150 patients ages 18-40 years with GDM. The group treatment consumed 40,000 IU of vitamin D and 8,000 IU of omega-3 2x/day, while the group control was given placebos. Researchers compared changes in blood sugar and blood lipid levels after 6 weeks.	The intervention group obtained decreased FBG (0.3±0.2 mmol/L), fasting insulin (1.0±0.6 uIU /mL), HOMA-IR (0.2±0.1 mmol/L), TGs (0.3±0.1 mmol/L), total cholesterol (0.5±0.2 mmol/L), LDL (1.1± 0.4 mmol/L), and VLDL (0.03±0.01 mmol/L). However, no found a difference in HDL change (p>0.05).
Lu et al.	USA	Evaluate the combination effect from take vitamin D at first pregnancy and late	Involved 806 (mother-daughter) pregnant women (asthmatic and not asthma) aged 18-39 years who are at risk tall have a child	The mother with asthma has a risk of 2x taller for having a child with recurrent asthma/wheezing at 3 years of

		pregnancy to incident recurrent asthma or wheeze in children	with asthma. Group treatment was given 4400 IU of vitamin D, meanwhile, group control was given a placebo (400 IU of vitamin D). Vitamin D levels were assessed at baseline gestation (10-18 weeks) and late gestation (32-38 weeks). Asthma status from a born child will be assessed at 6 years of age.	age. Mothers with asthmatics who get enough vitamin D at the start and the end of pregnancy could lower risk have a child with recurrent asthma/wheezing if compared with pregnant women who do not need vitamin D fulfilled (P for trend <0.001). This also applies when the child is 6 years old (P for trend = 0.04).
Levy et al.	Bangladesh	Evaluate variation in interindividual vitamin D levels in mothers and infants following supplementation during pregnancy and 6 months postpartum	1300 healthy pregnant women were divided into five groups and given vitamin D3 (cholecalciferol). Four groups were given doses 0.4200, 16800, 28.000 IU per week until 17-24 weeks of age pregnancy and continued with a placebo for up to 6 months postpartum. Group fifth gave a dose of 28000 IU per week from pregnancy until postpartum. Evaluation of cholecalciferol levels performed on the mother (moment pregnancy, labor, and 6 months postpartum) and infants (during born from blood rope center and baby 6 months old).	Supplemental intake of vitamin D and initial 25(OH)D donate a big part variation in maternal 25(OH)D moment delivery and postpartum (R2 = 70% and 79%). 25(OH)D pre-supplementation and vitamin D supplements dose are determinants mainly from response to maternal prenatal vitamin D intake.
Subramanian et al.	Bangladesh	Evaluate the effect of vitamin D dose-dependent during pregnancy on blood pressure in mid-late pregnancy	1257 pregnant women healthy without hypertension age 12-24 weeks of gestation divided becomes four groups based on vitamin D dosage there is given a placebo, low dose (4200 IU/ week), medium dose (16800 IU/ week), high dose (28000 IU/ week). Measurement of blood pressure is performed at 24 weeks, 30 weeks, and every week from 36 weeks until giving birth.	Vitamin D does not give an effect on SBP or DBP at age 24 or 30 weeks of pregnancy, higher blood pressure at 36 weeks in the cohort between high dose vs. placebo [mean difference (95% CI) mmHg: SBP = 2.3 (0.9–3.7); DBP = 1.9 (0.7–3.0)]. Got a difference small change in SBP and DBP between the vitamin D group and the placebo group (p>0.10). However, there is a big difference in the high dose group vs placebo at 30-36 weeks [SBP 0.2 (─ 0.1 to 0.5) and DBP 0.2 (─ 0.0 to 0.4) mmHg].

25(OH)D: 25-hydroxyvitamin-D, DBP: diastolic blood pressure, FBG: fasting blood glucose, GDM: gestational diabetes, HDL: high-density lipoprotein, HOMA-IR: homeostasis model assessment of insulin resistance, IU: international units, LDL: low-density lipoprotein, SBP: systolic blood pressure, TGs: triglycerides, VLDL: very-low-density lipoprotein

4. Discussion

Four articles are discussing the effect of vitamin D supplementation on blood pressure in pregnant women, the effective combination of vitamin D with omega-3 against gestational diabetes (GDM), the effect of vitamin D in pregnancy with or without asthma for recurrent asthma/wheezing in children, and assess variation interindividual vitamin D levels in mothers and infants. The fourth study was conducted in one developing country and two developed countries, while the pregnancy age for the subject was different.

4.1 Vitamin D Needs

Needs substance nutrition macro minerals and micro minerals during pregnancy must be fulfilled. One of the required microminerals is vitamin D which will decline around 5 ng/ml during pregnancy. Meanwhile, normal levels of vitamin D are 30-60 ng/ml. Vitamin D levels are knowns through serum concentrations of 25-hydroxyvitamin D (25(OH)D) (Fauzi, 2020). In line with research by Levy et al. (2021), Lu et al. (2021), dan Subramanian et al. (2021) who measured 25(OH)D concentration in the subjects to evaluate vitamin D levels in the blood. A study by Huang et al. (2021) mentioned that 1,25-dihydroxy vitamin D [1,25(OH)2D] is an active form of vitamin D for maintaining the stability system of innate and adaptive immunity. A low level of 25(OH)D can increase the risk of diseases such as psoriasis, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, tuberculosis, sepsis, and respiratory tract infection. Vitamin D also needs in the absorption process of calcium and phosphorus in the digestive tract. Increasing 1,25 dihydroxy vitamin D3 can provide an inline effect for calcium absorption in the intestine. Enhancement occurs 2-3 times during pregnancy that beneficial for bones and teeth in the mother and fetus (Suganda, 2021).

4.2 Vitamin D Deficiency

Vitamin D deficiency during pregnancy can raise negative effects on the mother and fetus because increasing the risk of preeclampsia, small-for-age pregnancy (SGA), premature birth, and GDM (Sari & Islamy, 2022). A study by Aji et al. (2019) has shown vitamin D deficiency occurs in 82.8% of pregnancies where one of the predisposition factors is sun exposure to less than 1 hour/per day. The average level of 25(OH)D is 13.15ng/mL (3.00-49.29ng/mL). In line with a study that states the average level of 25(OH)D is 13.6ng/mL, so it can conclude that vitamin D deficiency often occurs in pregnancy. There is a guess that vitamin D deficiency is most common in a four seasons country. However, it most commonly occurs in countries located in tropical zones such as South Asia and Southeast Asia. It is the impact of an imbalance between needs and intake. The need for vitamin D increases during pregnancy which adds to deficiency incidents, so vitamin D supplement intake becomes a recommendation (Judistiani et al., 2019).

4.3 Recommendation Dose of Vitamin D

Research results by Levy et al. (2021) state a variation of maternal 25(OH)D during labor and postpartum, also heterogeneity of vitamin D supplementation responses. It has been affected by two factors that are vitamin D supplementation consumption and early circulation of 25(OH)D. Other factors that can influence the 25(OH)D variations are biology and socio-demography factors. Vitamin D supplementation to prevent deficiency in pregnant women needs to consider a concentration of 25(OH)D in the population target. Nowadays, the intake recommendation of vitamin D for pregnant women is similar to adults who are unpregnant at the same age (10–15 µg/ day or 400–600 IU), reaching 25(OH)D of 25–50 nmol/ liter. Still, a lack of data that can explain any difference or not about vitamin D needs among pregnant and unpregnant women (Kiely et al., 2017). Research by Alhomaid et al. (2021) has found that there is no effect on obese

women and women who have low 25(OH)D levels at early pregnancy, where a low 25(OH)D level will be permanent during pregnancy and causes low 25(OH)D in newborns as well.

The Vitamin D recommendation for daily intake during pregnancy by the Institute of Medicine (IoM) is 600 IU because a dose of more than 28000 IU can raise the risk of hypercalciuria (Astuti & Adyani, 2020). In pregnant women who have vitamin D deficiency, the American College of Obstetricians and Gynecologists (ACOG) recommends consuming 1000–4000 IU per day (ACOG, 2011). However, some recommendations mention that consuming regular doses of 4000–6000 IU of vitamin D is safe for reaching optimal vitamin D levels (Blair, 2022). In this study, there are various doses of vitamin D for the research subject. A study by Lu et al. (2021) used vitamin D at a dose of 4400 IU, whereas other studies used the highest dose of 28000 IU (Levy et al., 2021; Subramanian et al., 2021) and 40000 IU for the intervention group (Huang et al., 2021).

4.4 The Benefits of Vitamin D

A study by Huang et al. (2021) has shown that pregnant women are also prone to experience omega-3 deficiency. So, their research used intervention to provide a combination of vitamin D and omega-3 fatty acids for six weeks in pregnant women with GDM. After six weeks, there is a significant decrease in FBG, insulin, HOMA-IR, TGs, total cholesterol, LDL, and VLDL levels. Vitamin D is very closely related to the metabolism of calcium and phosphorus which can decline blood sugar levels by influencing the insulin receptor. It is more effective with omega-3 combinations compared to vitamin D only. It is due to vitamin D directly affecting beta-cells pancreas that produces insulin. So, there is an association between vitamin D deficiency with blood sugar levels, changes in insulin concentrations, and tissue sensitivity for insulin targeted (Amraei et al., 2018). It is different from a study by Rodrigues et al. (2019) states there is not yet a study with good quality that can prove vitamin D supplementation for increasing the metabolism of glucose or exacerbate circumstances related to pregnancy and neonates with GDM. However, many studies have reported that low vitamin D levels during pregnancy increase the risk of GDM (Zhang et al., 2018). A meta-analysis study has shown a significant connection between vitamin D insufficiency against the enhancement risk of GDM 39% (Hu et al., 2018).

Previous studies state that pregnant women with GDM have a higher risk of experiencing preeclampsia. It occurs because the syndrome of insulin resistance in GDM can trigger the occurrence of oxidative stress which is also the pathogenesis of preeclampsia (Aulia et al., 2019). Research by Subramanian et al. (2021) has found vitamin D deficiency in pregnant women with preeclampsia. However, the result has shown no proven effect on SBP dan DBP when taking vitamin D from mid until the end of pregnancy, except if consumed at the highest dose of 28000 IU per week. In line with the study by Forde et al. (2021) has shown there is no significant connection between 25(OH)D levels with blood pressure in the population of healthy pregnant women. The same thing also happened in the combination of vitamin D and calcium. According to Heyden & Wimalawansa (2018), vitamin D helps maintain immune homeostasis and prevent vasoconstriction in the placenta and preeclampsia. Besides that, it could arrange the proliferation of endothelial cells and blood vessels, so the important role is settings blood pressure through the renin-angiotensin-aldosterone system.

The study by Lu et al. (2021) has found that a mother who gets enough vitamin D during pregnancy could reduce the risk of recurrent asthma/wheezing in their children. Vitamin D also can reduce exacerbation of asthma and respiratory infection. In line with the result of Wolsk et al. (2017) study that pregnant women with high levels of 25(OH)D could significantly decrease incidents of recurrent asthma/wheezing in children that occur in mothers with or without asthma. The studies explain that the development of the fetus's lungs in the first trimester is influenced by vitamin D status and affects the immune system during pregnancy. The ability of vitamin D as an immunomodulator can push the inflammation signal involved in cells related to asthma

response. However, other studies have found no existing effect of vitamin D on asthma repairment that involves pregnant women as the subject. It could be affected by the severity level of asthma or other confounding factors (Hall & Agrawal, 2017).

5. Conclusion

Based on this study, we have found that vitamin D has several benefits if its needs are sufficient during pregnancy. It can be beneficial for reducing the risk of recurrent asthma/wheezing in newborns from mothers with or without asthma, increasing FBG, fasting insulin, HOMA-IR, TGs, total cholesterol, LDL, and VLDL levels in pregnancy with GDM. However, the benefits of vitamin D are not proven in a change of SBP and DBP in early and mid-pregnancy. Giving a dose of Vitamin D supplementation should be considered 25(OH)D levels in each individual to prevent vitamin D deficiency in pregnant women because it can minimize the negative impact for both the mother and newborn. The researcher still finds inconsistency about the effect of vitamin D on pregnant women if comparing this result with similar research.

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