

Supplementation of Prenatal Vitamin D to Prevent Children's Stunting: A Literature Review

Sukmawati Sukmawati^{1,2,*}, Yanti Hermayanti^{2,*}, Eddy Fadlyana^{3,*}, Aep Maulid Mulyana^{4,*}, Furkon Nurhakim^{5,*}, Henny Suzana Mediani^{6,*}

¹Faculty of Medicine, Universitas Padjadjaran, Bandung, 40132, West Java, Indonesia; ²Department of Maternity Nursing, Faculty of Nursing, Universitas Padjadjaran, Bandung, 40132, West Java, Indonesia; ³Department of Child Health, Faculty of Medicine, Universitas Padjadjaran, Bandung, 40132, West Java, Indonesia; ⁴Faculty of Nursing, Universitas Padjadjaran, Bandung, 40132, West Java, Indonesia; ⁵Department of Fundamental Nursing, Faculty of Nursing, Universitas Padjadjaran, Bandung, 40132, West Java, Indonesia; ⁶Department of Pediatric Nursing, Faculty of Nursing, Universitas Padjadjaran, Bandung, 40132, West Java, Indonesia

*These authors contributed equally to this work

Correspondence: Henny Suzana Mediani, Department of Pediatric Nursing, Faculty of Nursing, Universitas Padjadjaran, Bandung, 40132, West Java, Indonesia, Tel +62 822-1739-1965, Email henny.mediani@unpad.ac.id

Background: Stunting is a common nutritional problem in children. Many risk factors contributing to stunting are identified in the literature. Vitamin D supplementation during pregnancy is useful for preventing impairment of fetal bone growth in the womb. However, lack of review in exploring supplementation of prenatal vitamin D is related to stunting in children.

Purpose: This study aims to identify the effectiveness of prenatal vitamin D supplementation in preventing stunting.

Methods: A literature review was conducted using PubMed, CINAHL, ScienceDirect, and Cochrane Library. Inclusion criteria were a randomized controlled trial study, published between 2011–2023, a full-text article for pregnant women and an independent variable supplement vitamin D to prevent children's stunting. The keywords used in English were "children OR child" AND "pregnant women" AND "preventive stunting" AND "vitamin D". Study quality was assessed using the Joanna Briggs Institute (JBI) appraisal tool.

Results: From the results of the study selection of 511 articles, 11 articles met the inclusion and eligibility criteria for study analysis. Four studies indicated that the administration of vitamin D did not influence the length of the neonate's body or the Length for Age Z-Score (LAZ), used as an indicator of stunting. However, seven articles demonstrated that providing vitamin D supplements to pregnant women impacted various aspects of anthropometry, including the length of the neonate's body. Our findings show that the dosage used of vitamin D in pregnancy varied between 1400–60,000 per week. Overall, results of this study analysis show that the intervention of prenatal vitamin D supplementation has an impact on the prevention of stunting.

Conclusion: This literature review highlighted the benefits of maternal vitamin D during pregnancy and for the children's growth. Prenatal vitamin D supplementation is needed to prevent stunting.

Keywords: children, pregnant women, stunting prevention, supplementation vitamin D

Introduction

Stunting remains a significant concern affecting children under the age of five on a global scale, particularly in low-income and developing nations. Stunting continues to be a prevalent nutritional issue in these regions.^{1–3} In 2019, approximately 21.3% of children under five worldwide were affected by stunting. Out of this percentage, 55% of stunted children were in the Asian region. This indicates a significant prevalence of stunting in Asia, highlighting the need for targeted interventions and efforts to address this issue.² Indonesia, as a developing country, faces a significant challenge with a high prevalence of stunting. Out of 88 countries worldwide, Indonesia ranks top three regarding stunting cases.^{1,4} Over the past decade, Indonesia has achieved significant advancements in decreasing the prevalence of childhood stunting. During this period, they managed to lower the rate from 37.2% in 2013 to 21.6% in 2022. The Indonesian government remains committed to further reducing this prevalence rate and has set a target of achieving a reduction of up to 14% by the year 2024.^{5,6} Lowering the stunting rate to 14% presents several challenges, including the substantial variation in stunting rates among different districts, insufficient support for

families to adopt appropriate feeding practices, and limitations in the capabilities of Community Health Cadres and Family Support Teams to identify malnutrition early and offer essential follow-up care.

Stunting has particularly significant impacts on children under the age of five. During this critical period of growth and development, the consequences of stunting can be particularly severe. Here are some of the key impacts of stunting on children under five. Stunting can hinder cognitive development during the early years of life.^{4,7} Moreover, Stunted children are more susceptible to a range of health issues, including increased risk of infections, diarrhea, and respiratory illnesses. These vulnerabilities can lead to frequent illnesses and hospitalizations. This indicates a pressing issue within the country, highlighting the need for focused strategies and interventions to address and reduce the prevalence of stunting among children.

Previous studies have identified numerous factors that contribute to stunting in children. Social, economic, environmental, and cultural conditions are determinant factors that contribute to intermediate factors.^{4,8} These factors include the fulfilment of maternal nutrition during pregnancy, both macronutrients and micronutrients, including vitamin D. The lack of nutritional intake during pregnancy, may cause stunting in children because the fetus in the womb requires adequate nutritional intake, both in quality and quantity, to support the process of fetal growth and development.⁹ The recommended daily intake of vitamin D for pregnant women is indeed 600 International Units (IU) per day. However, if a pregnant woman is found to be deficient in vitamin D, it is generally considered safe for healthcare professionals to prescribe a higher dose, typically in the range of 1000 to 2000 IU per day, to correct the deficiency.^{10,11} Pregnant women are particularly vulnerable to nutritional problems, which can have severe consequences for both the mother and the developing fetus. Inadequate nutrition during pregnancy can also result in long-term consequences, such as impaired newborn growth and development, compromised immune function, and increased susceptibility to various diseases.¹²

A high prevalence of vitamin D deficiency has been reported among pregnant women in various countries. The incidence of vitamin D deficiency varies from 18% to 84%.¹³ The high prevalence of vitamin D deficiency occurs in Middle Eastern countries, such as Iran, the United Arab Emirates and Saudi Arabia.¹⁴ Previous studies in Iran reported that around 75.1% of women suffer from vitamin D deficiency.^{14,15} Identifying the impact and benefits of vitamin D supplementation during pregnancy is important. Most women do not realize vitamin D is important during pregnancy and have little idea how much to take or what concentration to aim for.¹⁶

One of the efforts to prevent stunting is the administration of vitamin D3 supplements during pregnancy which can increase postnatal linear growth.¹⁷ Vitamin D plays a role in helping calcium absorption, and if calcium absorption is disturbed, bone mineralization will be disrupted and cause stunting.¹⁸ Vitamin D plays a crucial role in embryogenesis, particularly in fetal bone development and maintaining calcium balance during pregnancy.¹⁹ Furthermore, inadequate vitamin D levels in pregnancy have been linked to an increased risk of premature birth, where the baby is born before completing the full term of pregnancy. Identifying the impact and benefits of vitamin D supplementation during pregnancy is important. Most women do not realize vitamin D is important during pregnancy and have little idea how much to take or what concentration to aim for.^{16,20}

The conclusive information about improving and preventing stunting during the prenatal period requires additional study. A comprehensive study on nursing interventions for pregnant women can help nurses prevent and reduce the incidence of stunting. While previous studies have examined the impact of prenatal vitamin D supplementation on birth outcomes, understanding its effect on childhood stunting remains limited. Consequently, there is a need to investigate further the effectiveness of prenatal vitamin D intake in preventing stunting in young children. This study aims to fill this knowledge gap by examining the potential role of prenatal vitamin D supplementation in reducing the risk of stunting during early childhood. By exploring this relationship, the study seeks to provide valuable insights into the preventive strategies for stunting in young children and contribute to the existing body of knowledge in this field.

Materials and Methods

Study Design

This literature review followed the framework outlined by Arskey and O'Malley.²¹ This research framework has a broad conceptual scope, encompassing various relevant studies. It consists of five main stages: formulating research questions, identifying pertinent study findings, selecting studies, mapping data, and compiling, summarizing, and reporting the

results. The PRISMA Extension for Scoping Reviews (PRISMA-ScR) was utilized in this literature review to identify different topics that discuss interventions to prevent childhood stunting through prenatal Vitamin D supplementation (Figure 1). The research question guided the search: “How effective is Vitamin D supplementation for pregnant women in preventing stunting in young children?”

Search Strategy

The search process involved four databases: PubMed, CINAHL, ScienceDirect, and Cochrane Library. The following keywords and their synonyms were used: “children” AND “pregnant women”, AND “stunting”, OR “growth disorder”, AND “vitamin D.” Additionally, articles were searched using tags related to these keywords in Mendeley. The search was conducted in June 2023. Two authors (SS., and AMM.) identified studies on Mendeley’s reference management platform, and duplicate references were removed. The search process was repeated at least twice for each database to ensure comprehensive coverage, and the results were carefully checked and compared to ensure all relevant articles were included. The screening and selection of articles were based on key terms and subject headings.

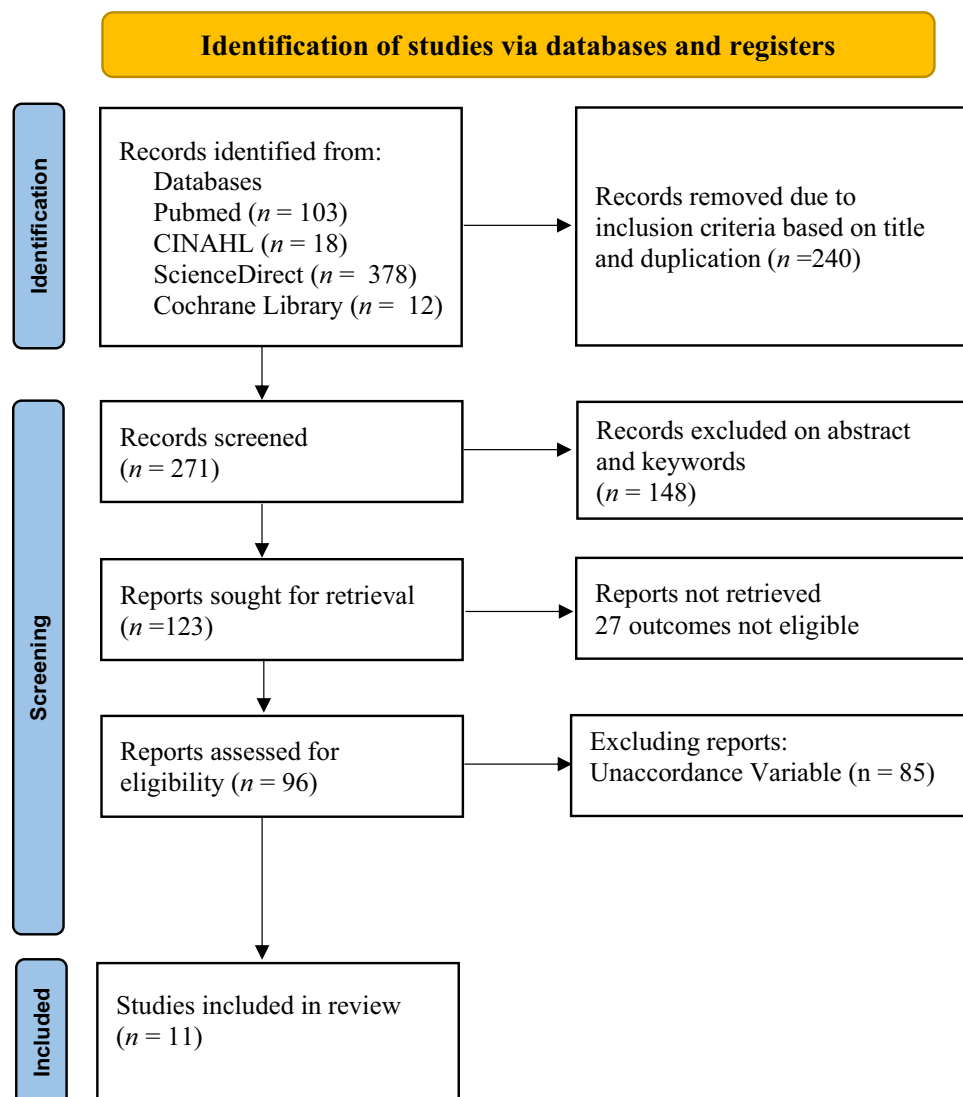


Figure 1 PRISMA Flow diagram.

Notes: Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.²²

Eligibility Criteria

The inclusion criteria for this study were as follows: the study had to be classified as a randomized controlled trial (RCT), publication of articles in 2011–2023, a full-text article, the study population had to involve pregnant women, and the independent variable being investigated had to be prenatal vitamin D supplementation to prevent children's stunting. Studies were excluded if not in the English language.

All selected literature in Mendeley was screened based on their titles and abstracts, a process that was repeated twice. Any inconsistencies identified were addressed thoroughly, and each selected article was read. The procedure was reviewed by two authors (SS., and HSM.).

Quality Appraisal

Critical appraisal is essential in assessing the strengths, weaknesses, and validity of the articles included in a study to determine their trustworthiness. Full-text articles were evaluated using the critical appraisal tools provided by the Joanna Briggs Institute (JBI).²³ These tools were utilized to assess the key methods, credibility, and relevance of the literature considered for inclusion. All authors extracted data specifically related to the effect of vitamin D supplementation on neonate body length from articles that fulfilled the JBI Critical Assessment Checklist requirements. Only those articles that scored above 80% based on the established criteria and their relevance to the topic were considered suitable for inclusion in the analysis (Table 1).

Data Collection and Analysis

In this study, a descriptive approach was employed for data analysis. The authors provided a descriptive account of the findings related to the supplementation of prenatal vitamin D. All authors participated in the study selection process, and the included studies were identified following the PRISMA flowchart, which involved steps such as identifying duplicates, filtering titles and abstracts, and assessing the availability of full-text articles.

Data Extraction

Data extraction in this study used the manual tabulation method. Identification of research characteristics includes items: research identity, country, research design, sample, population, gestational age, assessment tools, and interventions (Table 2). Extraction results from each article were analyzed, grouped based on demographic variable data and summary findings from each analyzed article, and presented in Tables 3 and 4.

Table 1 Critical Appraisal Tool

Study	JBI Critical Appraisal Tool
Kalra et al (2012) ²⁴	9/11 (81,82%)
Roth et al (2013) ²⁵	10/11 (90,90%)
Shakiba & Iranmanesh (2013) ²⁶	9/11 (81,82%)
Hossain et al (2014) ²⁷	10/11 (90,90%)
Hashemipour et al (2014) ²⁸	10/11 (90,90%)
Sablok et al (2015) ²⁹	10/11 (90,90%)
Mojibian et al (2015) ³⁰	9/11 (81,82%)
Vaziri et al (2016) ³¹	9/11 (81,82%)
Abotarobi et al (2017) ³²	9/11 (81,82%)
Motamed et al (2019) ³³	10/11 (90,90%)
Sudfeld et al (2022) ³⁴	10/11 (90,90%)

Table 2 Characteristic of Studies Reporting Supplementation of Prenatal Vitamin D to Prevent Children's Stunting (n = 11)

Study	Country	Sample	Population	Gestational age (Weeks)	Assessment Tools	Intervention
Kalra et al (2012) ²⁴	India	140	Pregnant women	12–24	ALP, neonatal serum Ca, and anthropometry measurement	Vitamin D
Roth et al (2013) ²⁵	Bangladesh	147	Pregnant women	26–30	Maternal serum samples of 25(OH)D measurement	Vitamin D
Shakiba & Iranmanesh (2013) ²⁶	Iran	51	Pregnant women	NA	Anthropometric measurements	Vitamin D
Hossain et al (2014) ²⁷	Pakistan	193	Pregnant women	20	Umbilical cord blood serum concentrations of 25(OH)D measurement	Vitamin D
Hashemipour et al (2014) ²⁸	Iran	130	Pregnant women	24–26	Weight neonatal, neonate length, neonate weight and neonatal head circumference measurements	Vitamin D
Sablok et al (2015) ²⁹	India	180	Pregnant women	14–20	Neonatal outcomes measurement	Vitamin D
Mojibian et al (2015) ³⁰	Iran	500	Pregnant women	12–16	LAZ	Vitamin D
Vaziri et al (2016) ³¹	Iran	127	Pregnant women	26–28	Neonates reach serum levels of 25(OH)D	Vitamin D
Abotarobi et al (2017) ³²	Iran	110	Pregnant women	22–26	Anthropometric measurement	Vitamin D
Motamed et al (2019) ³³	Iran	84	Pregnant women	Less than 12	Maternal weight gain, neonate length, neonatal weight and neonatal head circumference	Vitamin D
Sudfeld et al (2022) ³⁴	Tanzania	1,148	Pregnant women	12–27	LAZ	Vitamin D

Abbreviations: LAZ, length-for-age z-score; RCT, Randomized Controlled Trials; ALP, Alkaline phosphatase; 25OHD, 25-hydroxyvitamin D.

Table 3 Supplementation of Prenatal Vitamin D to Prevent Children's Stunting by Demographic Variable in Selected Studies

Components	Number of Studies (N)	Sample Size (N)	Percentage (%)
Overall Studies	11	2,810	100
Publishing Year			
2012	1	140	5.0
2013	2	198	7.04
2014	2	323	11.49
2015	2	680	24.19
2016	1	127	4.51

(Continued)

Table 3 (Continued).

Components	Number of Studies (N)	Sample Size (N)	Percentage (%)
2017	1	110	4.0
2019	1	84	3.0
2022	1	1,148	40.85
Country			
Bangladesh	1	147	5.23
India	2	320	11.38
Iran	6	1,002	35.65
Pakistan	1	193	6.86
Tanzania	1	1,148	40.85
Study Design			
RCT	11	2,810	100
Gestational Age			
< 12 weeks	1	84	3.0
12–28 weeks	9	2,546	90.60
> 28–36 weeks	1	180	6.40
Assessment tools			
ALP, neonatal serum Ca and anthropometry measurement	1	140	5.0
LAZ	2	1,331	47.36
Neonates reach serum levels of 25(OH)D	1	51	1.81
Maternal serum samples of 25(OH)D measurement	1	193	6.86
Weight neonatal, neonate length, neonate weight and neonatal head circumference measurements	1	130	4.62
Neonatal outcomes. measurement	1	180	6.40
Anthropometric measurements	2	627	22.31
Maternal weight gain during pregnancy, neonate length, neonatal weight, and neonatal head circumference.	1	110	4.0
Umbilical cord blood serum concentrations of 25(OH)D measurement	1	84	3.0

Abbreviations: LAZ, length-for-age z-score; RCT, Randomized Controlled Trials; ALP, Alkaline phosphatase; 25OHD, 25-hydroxyvitamin D.

Results

Description of Study Selection

The authors initially identified 511 articles from the four databases: PubMed, CINAHL, ScienceDirect, and Cochrane Library. To eliminate duplicates, the authors utilized the Mendeley application, which removed 240 duplicate articles. This left a total of 271 articles for the selection process. The authors then proceeded to screen the articles based on the inclusion criteria, initially reviewing the titles and abstracts. From this screening, 123 articles were identified to be read in full by the

Table 4 Summary of Findings Related to the Impact of Supplementation of Vitamin D to Prevent Children's Stunting (n=11)

Study	Study Objective	Treatment and Procedure	Dose per Weeks (IU)	Findings
Kalra et al (2012) ²⁴	To evaluate the effects of administering 1500 mg of vitamin D to pregnant women during the second trimester and 3000 mg of vitamin D during the second and third trimesters on two main outcomes: maternal serum calcemic status and anthropometry of newborns	Administration of vitamin D 1500 mg to pregnant women in the second trimester and administration of vitamin D 3000 mg in the second and third trimesters, 25-hydroxy vitamin D (25(OH) D) in pregnant women at term. Cord blood (CB), alkaline phosphatase (ALP), neonatal serum Ca and anthropometry were measured in mothers-infant.	1.416	The results showed that administering 1500 mg of vitamin D during the second trimester and 3000 mg of vitamin D during the second and third trimesters significantly increased pregnant women's 25-hydroxyvitamin D levels and calcium.
Roth et al (2013) ²⁵	To examine the effects of prenatal vitamin D supplementation on infant growth	The pregnant woman was given 4000 IU of vitamin D3 supplementation daily, starting at 20 weeks of gestation until delivery. Maternal serum samples of 25-hydroxyvitamin D (25OHD) were assessed at the start of the intervention, and the neonate's vit D status was assessed in cord blood or neonatal serum samples within 48 hours of birth.	28.000	Study findings show that vitamin D3 supplementation at a dose of 35,000 IU per week in pregnant women during the third-trimester results in an increase in the linear growth of the infant.
Shakiba & Iranmanesh (2013) ²⁶	To identify the optimal dosage of vitamin D required during pregnancy to achieve a vitamin D level greater than 20 ng/mL in neonates	The intervention group received two 1000 IU (2000 IU) vitamin D3 pills daily from weeks 26–28 until delivery. mother serum 25-hydroxy vitamin D was assessed, anthropometric measurements of the infant (at birth, 4th and 8th weeks postpartum), and parameters of maternal and infant bone mass examination	14.000	After the intervention of giving vitamin D to pregnant women, it was found that neonates from 76% of the participants had sufficient levels of 25 (OH)D. in addition, no side effects were observed in our participants during the vitamin D supplementation period.
Hossain et al (2014) ²⁷	To examine how the administration of vitamin D supplements to pregnant women and the health of newborn infants	Pregnant women on a routine care regimen received an oral liquid formulation (400 IU/drop) of vitamin D3 at 4000 IU (10 drops daily) starting from 20 weeks gestation.	28.000	Studies show that maternal vitD supplementation improves maternal and infant vitD status. Postpartum, maternal 25OHD was increased, neonatal 25OHD levels were high, APGAR scores at one and 5 minutes were significantly higher, and neonatal anthropometric parameters were normal.
Hashemipour et al (2014) ²⁸	To investigate the potential impact of treating vitamin D deficiency in pregnant women on various measures of fetal growth	The pregnant woman received 200 mg of calcium, a multivitamin (vitamin D3 400 U) daily, and vitamin D3 (50,000 U) for eight weeks.	2.800	There is an independent correlation of supplementation of low serum vitamin D in pregnant women on maternal weight gain, neonatal weight and length, and neonatal head circumference (p-value < 0.05)

(Continued)

Table 4 (Continued).

Study	Study Objective	Treatment and Procedure	Dose per Weeks (IU)	Findings
Sablok et al (2015) ²⁹	To investigate the effect of supplementation with cholecalciferol (a form of vitamin D) in improving vitamin D levels in pregnant women	Pregnant women received vitamin D supplementation with one dose of 60,000 IU at 20 weeks gestation. These women did not receive two doses of 120,000 IU at 20 and 24 weeks gestation. Pregnant women with low levels received four doses of cholecalciferol 120,000 IU at 20, 24, 28 and 32 weeks gestation.	60.000	Vitamin D supplementation reduces the risk of maternal comorbidities and helps improve neonatal outcomes. Newborn mothers in group A had lower cord blood 25(OH)-D levels compared to group B (mean 43.11 ± 81.32 nmol/l vs 56.8 ± 47.52 nmol/l). They also had an average lower birth weight of 2.4 ± 0.38 kg compared to group B of 2.6 ± 0.33 kg.
Mojibian et al (2015) ³⁰	To examine the effects of supplementation with a high dose of vitamin D (50,000 IU) on pregnancy and neonatal outcomes	In the third trimester, pregnant women were given vitamin D3 (35,000 IU/week; vitamin D). Anthropometric examination performed at birth, 1, 2, 4, 6, 9, and 12 months.	35.000	This study found that the average level of 25(OH)D (vitamin D) in cord blood increased significantly. The reported specific value is 37.9 ± 18 ng/mL. Although vitamin D levels in cord blood varied, there were no significant differences in measured anthropometric parameters, such as weight, length, or head circumference, among neonates.
Vaziri et al (2016) ³¹	To examine the impact of daily supplementation with 2000 IU of vitamin D during the later stages of pregnancy on the anthropometric measurements of infants and the mother's and infant's bone mass parameters.	Pregnant women received two 1000IU vitamin D ₃ pills (2000IU) daily from weeks 26–28 until childbirth. Maternal serum 25-hydroxyvitamin D, infants' anthropometric measurements (at birth, 4th and 8th weeks postnatal), and maternal and infant bone mass parameters were examined.	1.400	The study found that daily supplementation with 2000 IU of vitamin D3 during late pregnancy did not result in significant changes in the anthropometric measurements of the baby from birth to the 8th week after birth.
Abotarobi et al (2017) ³²	To examine the impact of vitamin D treatment on maternal and neonatal indicators in pregnant women who were diagnosed with hypocalcemia	Pregnant women are given daily cholecalciferol (25 (OH)D), 600 IU or 3000 IU, from 15 –18 weeks of gestation until delivery. And maternal chemistry was assessed during the third trimester and at delivery. At one month, neonatal anthropometric variables, bone mass and fat, were assessed by dual-energy X-ray absorptiometry scanning.	4.200	The administration of vitamin D did not significantly affect the average serum calcium levels in pregnant women and neonates. Furthermore, there were no notable differences in neonatal weight, height, or head circumference between the intervention and control groups. However, the influence on the neonate appears to depend highly on the extent of vitamin D deficiency in pregnant women.

Motamed et al (2019) ³³	To assess the effectiveness of two doses of vitamin D3 supplementation administered during pregnancy and their impact on maternal and cord blood vitamin D levels, inflammatory biomarkers, and maternal and neonatal outcomes.	Pregnant women with vitamin D insufficiency received (200 mg) of calcium plus vitamin D3 (400 U) daily and vitamin D3 (50,000 U) for eight weeks each. At delivery, maternal and umbilical cord blood 25(OH)D levels, maternal weight gain, neonate length, neonatal weight and neonatal head circumference were measured.	1.400	Vitamin D3 supplementation at 2000 IU/day has increased neonatal weight, length, and head circumference.
Sudfeld et al (2022) ³⁴	To examine the effect of vitamin D3 supplementation on maternal and infant health outcomes	Participants receive daily 3000 IU vitamin D3 supplements or matching placebo supplements from the second trimester of pregnancy (12–27 weeks) until one year postpartum.	21.000	There was no difference in the risk of infant stunting at one year of age between the vitamin D3 (407 events among 867 infants) and placebo groups (413 events among 873 infants) (relative risk 1.00, 95% CI 0.92 to 1.10, p = 0.95).

Abbreviation: 25OHD, 25-hydroxyvitamin D.

authors. The authors carefully read the full text of these 123 articles and ultimately selected 11 articles that aligned with the review's objectives (Figure 1). Then, the articles were analyzed using the JBI Critical Appraisal Tool assessment.

Characteristics of Study

Included studies obtained Randomized Controlled Trials (n=11). This study's total sample of participants was 2.810. The studies included were conducted in Iran (n= 6), Pakistan (n= 1), Bangladesh (n= 1), India (n= 2), and Tanzania (n= 1). Nine instruments were used in the study analyzed (Table 2).

Most studies occurred from 2013 to 2015, each representing 18% of the total. However, there was variation in sample sizes, ranging from 51 to 1.148 pregnant women. The publications included pregnant women, with the majority having a gestational age which is divided into three categories, namely < 12 weeks (n= 1), 12–28 weeks (n= 9), dan > 28–36 weeks (n= 1) (Table 3).

The Effectiveness of Supplementation Prenatal Vitamin D in Preventing Stunting

Based on the analysis of seven studies, the intervention of administering vitamin D has a significant impact on the prevention of stunting.^{24,34} This conclusion is supported by the results of various statistical tests such as the Kruskal–Wallis test, Mann–Whitney *U*-test, and Spearman's test, as well as measurements of anthropometry including weight, height, head circumference, and Dual X-ray absorptiometry. However, four studies indicated that the administration of vitamin D did not influence the length of the neonate's body or the Length for Age Z-Score (LAZ), used as an indicator of stunting.^{27,33} Nonetheless, seven articles demonstrated that providing vitamin D supplements to pregnant women impacted various aspects of anthropometry, including the length of the neonate's body.^{24,34} Our analysis of this study revealed that the dosages used in vitamin D administration during pregnancy ranged widely, with doses ranging from 1400 to 60,000 units per week. Overall, this review of randomized controlled trial (RCT) studies provides evidence that inadequate dietary vitamin D intake among pregnant women can contribute to stunting in children (Table 4).

Discussion

Principal Finding

The Role of Vitamin D in the Prenatal Period

This research highlights the potential impact of prenatal vitamin D supplementation in lowering the risk of childhood stunting. Among the nutrients that were found to be associated with a decreased incidence of stunting, vitamin D stood out. Vitamin D plays a crucial role in regulating bone mineral metabolism and bone development. It's worth noting that vitamin D supplements can influence bone length by modulating thyroid hormone levels.³⁵ Vitamin D is a steroid hormone that plays a crucial role in bone metabolism and the maintenance of calcium homeostasis. Active vitamin D, also known as 1,25-dihydroxyvitamin D (1,25(OH)₂D), has several important functions in the endocrine system. It collaborates with parathyroid hormone and calcitonin to regulate calcium and phosphorus levels in the bloodstream, thereby increasing the concentration of calcium and phosphorus in the blood plasma. This coordinated regulation is vital for the development and maintenance of strong and dense bones. Vitamin D also has a significant impact on the growth hormone (GH) and insulin-like growth factor-1 (IGF-1) pathways, further influencing tissue growth. GH operates by stimulating the differentiation and proliferation of chondrocytes (cartilage cells) and osteoblasts (bone-forming cells), while IGF-1 reduces osteoblast cell death (apoptosis) and promotes the formation of new osteoblasts, ultimately contributing to bone formation.³⁶

Inadequate vitamin D intake can lead to vitamin D deficiency, which can have detrimental effects on bone mineralization, especially during childhood. When the body lacks sufficient vitamin D, its ability to bind to vitamin D receptors in the bones is compromised. This, in turn, can slow down the rate of bone growth, leading to decreased linear growth and potentially resulting in stunted growth. Therefore, vitamin D deficiency can indeed interfere with proper bone development and contribute to the condition of stunting in children.³⁷

Vitamin D plays a crucial role during the prenatal period, both for the mother and the developing baby. Vitamin D is essential for developing the baby's bones and teeth. It helps the mother's body absorb calcium, which is necessary to mineralize and grow the baby's skeleton. Sufficient vitamin D levels are crucial to prevent conditions like rickets and

skeletal deformities in the baby. Vitamin D also plays an essential role in modulating the immune system, which is particularly important during pregnancy.¹⁹ It helps regulate immune responses, supports the function of immune cells, and may reduce the risk of infections for both the mother and the developing baby.

Vitamin D is essential for the growth of children. Children need a higher calcium intake than adults for normal calcification of the growth plate and bone mineralization.³⁸ Vitamin D contributes to bone mineralization by maintaining normal calcium and phosphate concentrations in the blood.³⁹ Moreover, vitamin D raises the growth plate cells' sensitivity to growth hormones, which impacts the linear growth of children.³⁸

Vitamin D supports overall maternal and fetal health. Vitamin D is involved in various biological processes that contribute to overall health. It helps maintain cardiovascular health, regulates gene expression, supports brain development, and may have a role in reducing the risk of certain pregnancy complications.

Vitamin D plays a significant role in both the growth of babies and postnatal development. The daily recommended intake of vitamin D for pregnant women is 600 IU, which is equivalent to 15 micrograms (mcg), with 1 mcg containing 40 IU. If a pregnant woman is found to have a deficiency in vitamin D, it is generally considered safe to provide a higher dose, typically in the range of 1000 to 2000 IU. It's important to note that the Institute of Medicine Recommended Dietary Allowance (RDA) for Pregnancy suggests a lower dose of 15 IU, which is relatively small compared to the higher doses recommended for addressing deficiencies.⁴⁰

This study emphasizes the link between childhood stunting and vitamin D deficiency during pregnancy. Vitamin D deficiency during pregnancy can have a detrimental effect on the child's bone growth. As a result, providing vitamin D supplementation to pregnant women has emerged as a new intervention strategy to mitigate potential adverse effects on pregnancy. Adequate vitamin D supplementation during pregnancy serves to meet the growing fetus's increased calcium requirements, which are vital for proper growth and development. Consuming foods rich in vitamin D, such as eggs, fish, fish oil, and vitamin D-fortified milk, as well as exposure to sunlight, can help pregnant women meet their vitamin D needs.⁴¹ Supplying adequate vitamin D supplementation during pregnancy plays a crucial role in meeting the increased calcium needs of the developing fetus, supporting its growth and development. Consuming foods rich in vitamin D can help fulfill the maternal vitamin D requirements during pregnancy. These dietary sources include eggs, fish, fish oil, and milk fortified with vitamin D. Additionally, exposure to sunlight is another important natural source of vitamin D production in the body.¹¹

Vitamin D and Stunting in Young Children

Vitamin D deficiency has been linked to stunted growth in children. Stunting is a condition where children experience impaired growth and end up shorter in height compared to the average age group. Vitamin D plays a crucial role in calcium absorption from the diet. Calcium is essential for the development and mineralization of bones. Insufficient vitamin D levels can lead to poor calcium absorption and inadequate bone mineralization, contributing to stunted growth in children.

Maternal vitamin D deficiency has been associated with a greater risk of stunting among neonates and children. Supplementation of 1500 IU and two doses of 3000 IU of vitamin D3 in pregnant women has a beneficial effect on infant body length.^{24,42} Pregnant women, after being given vitamin D3 4000 IU supplementation every day from 20 weeks of pregnancy until delivery, improve maternal vitamin D status and neonatal anthropometry.²⁷ Maternal vitamin D deficiency has been associated with adverse effects on the newborn's bone, cardiovascular, respiratory, and neurological function.⁴³ Decreased 25OHD levels in pregnant women early (19 weeks) of gestation are associated with an increase in the fetal femoral strain index, proven as early as 19 weeks.⁴² Giving vitamin D supplementation 2000 IU/day to pregnant women is effective in increasing the baby's weight, body length and head circumference compared to 1000 IU.³³

Another study found that children whose mothers were supplemented with doses of vitamin D during pregnancy showed a significant increase in birth length (p -value < 0.001).²⁵ Pregnant women with calciferol deficiency received a supplement of 120,000 IU at 20 weeks, 24 weeks, 28 weeks and 32 weeks. Treatment of low serum vitamin D during pregnancy increased fetal growth index and maternal weight gain, fetal growth index and maternal weight gain.²⁹ Administration of vitamin D 35000 IU/week in 3rd-trimester pregnant women reduces the risk of maternal comorbidities and helps improve neonatal outcomes.²⁵ 3rd-trimester pregnant women with vitamin D deficiency, after receiving vitamin D supplements > 50,000 IU, their neonates reach serum levels of 25(OH)D > 20 ng/mL.²⁶ Based on these

studies identified that supplementation of higher doses of vitamin D during the prenatal period is important, especially at the beginning of the second trimester of pregnancy, especially for vitamin D-deficient pregnant women to reduce a negative outcome in both neonates and their mothers.

This fact can be explained by the greater transfer of 25(OH)D to the fetus via the transplacental route in the last months of pregnancy, which is the main source of this vitamin to newborns in their first months. In addition, the placenta contains a vitamin D receptor and produces the enzyme 1 α -hydroxylase, which converts 25(OH)D to its active form and, consequently, increases the supply of vitamin D to the fetus.

Interestingly, four articles state that vitamin D supplements do not affect the length of the neonate's body.^{28,32,36,44} The ineffectiveness of vitamin D administration can also be caused by non-modifiable factors such as genetics, race, gender, and hormonal factors.³⁹ The duration of vitamin D administration can also cause the absence of significant differences in the two groups.⁴⁵ It is possible due to administering lower doses of vitamin D for pregnant women who are not severely vitamin D deficient or pregnant women who obtain vitamin D from other sources such as foods and skin exposure to the sun.

Vitamin D plays several roles in all stages of pregnancy, from implantation to delivery. Vitamin D deficiency in the mother has been associated with adverse effects on the newborn's bone, cardiovascular, respiratory, and nervous functions, as well as decreased birth weight and neonatal length, delayed fontanel closure, fontanel and increased risk of neonatal infection.^{39,43} Vitamin D helps harden bones by regulating calcium and phosphorus in the blood to be deposited in the process of bone hardening. One of the active forms of vitamin D is calcitriol which increases calcium and phosphorus levels in plasma, thereby maintaining normal conditions so that bone mineralization is maintained.⁴⁶ Vitamin D supplementation in pregnant women positively impacts fetal cell mass and function, bone mineralization and metabolism.³²

Lack of vitamin D supplementation during pregnancy may potentially impact neonates. Vitamin D controls genes responsible for placenta amino-acids transporters. Meanwhile, amino acids are important for fetal soft tissues and bone matrix growth. So, vitamin D may influence fetal growth.²⁴ Thus, persistent vitamin D insufficiency deteriorates transcriptional regulation of skeletal homeostasis and linear growth, which may cause childhood stunting.

It's worth noting that stunting is a complex issue influenced by multiple factors, including nutrition, overall health, socioeconomic conditions, and access to healthcare. While vitamin D deficiency can contribute to stunting, it is often one piece of a larger puzzle. Providing children with a balanced and nutritious diet, including foods rich in vitamin D, and ensuring adequate sun exposure can help prevent vitamin D deficiency and support healthy growth and development.^{46–48}

Strength and Limitations

While it should be noted that the studies included in this literature review were limited to those conducted in Asia and Africa, it is important to acknowledge that the findings cannot be generalized worldwide. However, the results of this study do suggest that administering adequate levels of vitamin D to pregnant mothers can contribute to an increase in the weight, body length, and head circumference of babies during the pregnancy phase. Meanwhile, inadequate dietary vitamin D intake among pregnant women can contribute to stunting in children.

Conclusion

This review underscores the significance of pregnant women incorporating vitamin D supplements into their nutrition during pregnancy, as it has a discernible impact on the anthropometric measurements of newborns. Prenatal vitamin D supplementation emerges as a crucial factor that can be adjusted to prevent stunting, support metabolic processes, promote bone growth, and maintain calcium balance.

The results of this review provide valuable insights that can be incorporated into interventions aimed at managing the care of pregnant women and improving infant anthropometric outcomes. One such intervention involves administering vitamin D as a nutritional supplement during pregnancy. Healthcare professionals, including nurses, play a crucial role in preventing stunting in children by educating pregnant women about the significance of vitamin D intake during pregnancy. Nurses and other healthcare providers can play a pivotal role in raising awareness about the importance of proper nutrition and vitamin D supplementation during pregnancy. This education can empower pregnant women to make informed choices that positively impact their own health and the health of their infants, contributing to better anthropometric outcomes and overall well-being.

Acknowledgments

The authors appreciated the Universitas Padjadjaran for facilitating the database in conducting this literature review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest.

References

1. UNICEF. Undernutrition contributes to nearly half of all deaths in children under 5 and is widespread in Asia and Africa. Unicef; 2016.
2. Kemenkes RI. Situasi Balita Pendek (Stunting) di Indonesia [Situation of Short Toddlers (Stunting) in Indonesia]. Kementerian Kesehat RI; 2018. Indonesian.
3. World Health Organization (WHO). Maternal, infant, and young child nutrition. *WHO*. 2019;266(EB146/24):1–9.
4. Mediani HS, Hendrawati S, Pahria T, Mediawati AS, Suryani M. Factors affecting the knowledge and motivation of health cadres in stunting prevention among children in Indonesia. *J Multidiscip Healthc*. 2022;15(May):1069–1082. doi:10.2147/JMDH.S356736
5. Kemenkes. Hasil Survei Status Gizi Indonesia (SSGI) 2022 [Results of the 2022 Indonesian Nutrition Status Survey]; 2023. Available from: <https://upk.kemkes.go.id/new/kementerian-kesehatan-rilis-hasil-survei-status-gizi-indonesia-ssgi-tahun-2022>. Accessed 25 October 2023.
6. Badan Kependudukan dan Keluarga Berencana Nasional Kebijakan dan Strategi Percepatan Penurunan Stunting di Indonesia [Policies and Strategies to Accelerate Stunting Reduction in Indonesia]. *Modul Train Train*. 2021;1(1):233–240. Indonesian.
7. Dasman H. Empat dampak stunting bagi anak dan negara Indonesia [Four impacts of stunting on children and the country of Indonesia]. *Conversat*. 2019;1:2–4. Available from: <http://repo.unand.ac.id/21312/1/EmpatdampakstuntingbagianakdannegaraIndonesia.pdf>. Accessed 18 October 2023.
8. Goudet SM, Bogin BA, Madise NJ, Griffiths PL. Nutritional interventions for preventing stunting in children (Birth to 59 months) living in urban slums in low-and middle-income countries (LMIC). *Cochrane Database Syst Rev*. 2019;2019(6). doi:10.1002/14651858.CD011695.pub2
9. Kemenkes RI. Pedoman Strategi Komunikasi Perubahan Perilaku Dalam Percepatan Pencegahan Stunting Di Indonesia [Guidelines for Communication Strategy for Behavior Change in Accelerating Stunting Prevention in Indonesia]; 2018. Indonesian. Available from: <https://ayosehat.kemkes.go.id/buku-pedoman-strakom-percepatan-pencegahan-stunting-di-indonesia>. Accessed 25 October 2023.
10. Kemenkes RI. Peraturan Menteri Kesehatan Republik Indonesia Nomor 28 Tahun 2019 Tentang Angka Kecukupan Gizi Yang Dianjurkan Untuk Masyarakat Indonesia [Regulation of the Minister of Health of the Republic of Indonesia Number 28 of 2019 concerning Recommended Nutritional Adequacy Rates for Indonesian People]; 2019. Indonesian. Available from: <http://www.scopus.com/inward/record.url?eid=2-s2.0-84865607390&partnerID=tZ0tx3y1>. Accessed October 18, 2023.
11. Paramita F. Gizi Pada Kehamilan [Nutrition in Pregnancy]; 2019. Available from: <https://fik.um.ac.id/wp-content/uploads/2020/10/22.-GIZI-PADA-KEHAMILAN.pdf>. Accessed 25 October 2023. Indonesian
12. Senbanjo IO, Olayiwola IO, Afolabi WA, Senbanjo OC. Maternal and child under-nutrition in rural and urban communities of Lagos state, Nigeria: the relationship and risk factors. *BMC Res Notes*. 2013;6(1). doi:10.1186/1756-0500-6-286
13. Hajizadeh S, Shary JR, Reed SG, Wagner CL. The prevalence of hypovitaminosis D and its risk factors in pregnant women and their newborns in the Middle East: a systematic review. *Int J Reprod Biomed*. 2019;17(10):685–708. doi:10.18502/ijrm.v17i10.5284
14. Mirhashemi S, Kalantar Motamed MH, Mirhashemi AH, Taghipour H, Danial Z. Vitamin D deficiency in Iran. *Int J Med Rev*. 2017;4(3):64–65. doi:10.29252/ijmr-040301
15. Sepandi M, Esmailzadeh S, Hosseini MS. Prevalence of vitamin D Deficiency among Iranian pregnant women. *Nutr Diet Suppl*. 2020; Volume 12:97–102. doi:10.2147/NDS.S261229
16. Grant WB, Grant WB. Targeted 25-hydroxyvitamin D concentration measurements and vitamin D3 supplementation can have important patient and public health benefits Targeted 25-hydroxyvitamin D concentration measurements and vitamin D 3 supplementation can have important patient. *Eur J Clin Nutr*. 2020;74(3):366–376. doi:10.1038/s41430-020-0564-0
17. Suntari Y, Ermiani E, Harun H. Intervensi masalah nutrisi pada masa kehamilan: studi literatur [Intervention of nutritional problems during pregnancy: literature study]. *Ris Inf Kesehat*. 2020;9(1):22. Indonesian. doi:10.30644/rik.v9i1.254
18. Chairunnisa E, Kusumastuti AC, Panunggal B. Asupan Vitamin D, Kalsium Dan Fosfor Pada Anak Stunting Dan Tidak Stunting Usia 12-24 Bulan Di Kota Semarang [Intake of Vitamin D, Calcium and Phosphorus in Stunted and Not Stunted Children Aged 12-24 Months in Semarang City]. *J Nutr Coll*. 2018;7(1):39. Indonesian. doi:10.14710/jnc.v7i1.20780
19. Weinert LS, Silveiro SP. Maternal–fetal impact of vitamin D deficiency: a critical review. *Matern Child Health J*. 2015;19(1):94–101. doi:10.1007/s10995-014-1499-7
20. Alaofè H, Asaolu I. Maternal and child nutrition status in rural communities of Kalalé District, Benin: the relationship and risk factors. *Food Nutr Bull*. 2019;40(1):56–70. doi:10.1177/0379572118825163
21. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol Theory Pract*. 2005;8(1):19–32. doi:10.1080/1364557032000119616
22. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71

23. JBI. Critical appraisal tools. The Joanna Briggs Institute; 2017. Available from: <https://jbi.global/critical-appraisal-tools>. Accessed August 11, 2022.
24. Kalra P, Das V, Agarwal A, et al. Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant. *Br J Nutr*. 2012;108(6):1052–1058. doi:10.1017/S0007114511006246
25. Sudfeld CR, Manji KP, Muihi A, et al. Vitamin D 3 supplementation during pregnancy and lactation for women living with HIV in Tanzania: A randomized controlled trial. *PLoS Medicine*. 2022;19(4):e1003973. doi:10.1371/journal.pmed.1003973
26. Shakiba M, Iranmanesh MR. Vitamin D requirement in pregnancy to prevent deficiency in neonates: a randomised trial. *Singapore Med J*. 2013;54(5):285–288. doi:10.11622/smedj.2013110
27. Hossain N, Kanani FH, Ramzan S, et al. Obstetric and neonatal outcomes of maternal vitamin D supplementation: results of an open-label, randomized controlled trial of antenatal vitamin D supplementation in Pakistani women. *J Clin Endocrinol Metab*. 2014;99(7):2448–2455. doi:10.1210/jc.2013-3491
28. Hashemipour S, Ziaee A, Javadi A, et al. Effect of treatment of vitamin D deficiency and insufficiency during pregnancy on fetal growth indices and maternal weight gain: a randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2014;172(1):15–19. doi:10.1016/j.ejogrb.2013.10.010
29. Sablok A, Batra A, Thariani K, et al. Supplementation of Vitamin D in pregnancy and its correlation with feto-maternal outcome. *Clin Endocrinol*. 2015;83(4):536–541. doi:10.1111/cen.12751
30. Mojibian M, Soheilykhah S, Zadeh MAF, Moghadam MJ. Maternal, infant and young child nutrition. *Int J Reprod Biomed*. 2015;13(11):687–696.
31. Vaziri F, Dabbaghmanesh MH, Samsami A, Nasiri S, Shirazi PT. Vitamin D supplementation during pregnancy on infant anthropometric measurements and bone mass of mother-infant pairs: a randomized placebo clinical trial. *Early Hum Dev*. 2016;103:61–68. doi:10.1016/j.earlhumdev.2016.07.011
32. Abotorabi S, Poor SH, Esmailzadehha N, Ziaee A, Khoeiniha MH. Effect of treatment with vitamin D on maternal and neonatal indices in pregnant women with hypocalcemia: a randomized controlled trial. *Int J Pediatr*. 2017;5(9):5733–5739. doi:10.22038/ijp.2017.22146.1851
33. Motamed S, Nikooyeh B, Kashanian M, Hollis BW, Neyestani TR. Efficacy of two different doses of oral vitamin D supplementation on inflammatory biomarkers and maternal and neonatal outcomes. *Matern Child Nutr*. 2019;15(4):1–11. doi:10.1111/mcn.12867
34. Sudfeld CR, Manji KP, Muihi A, et al. Vitamin D 3 supplementation during pregnancy and lactation for women living with HIV in Tanzania: a randomized controlled trial. *PLoS Med*. 2022;19(4):1–20. doi:10.1371/journal.pmed.1003973
35. Roth DE, Gernand AD, Morris SK, et al. Maternal vitamin D supplementation during pregnancy and lactation to promote infant growth in Dhaka, Bangladesh (MDIG trial): study protocol for a randomized controlled trial. *Trials*. 2015;16(1):1–17. doi:10.1186/s13063-015-0825-8
36. Fakhira FS, Garna H, Hadiati DE. Literature Review: pengaruh Defisiensi Vitamin D terhadap Proses Pertumbuhan Tulang pada Balita Stunting [Literature Review: the effect of Vitamin D Deficiency on the Bone Growth Process in Stunted Toddlers]. *Bandung Conf Ser Med Sci*. 2023;3(1):859–864. Indonesian. doi:10.29313/bcsms.v3i1.6751
37. Lee JY, So TY, Thackray J. A review on vitamin D deficiency treatment in pediatric patients. *J Pediatr Pharmacol Ther*. 2013;18(4):277–291. doi:10.5863/1551-6776-18.4.277
38. Shin YH, Shin HJ, Lee YJ. Vitamin D status and childhood health. *Korean J Pediatr*. 2013;56(10):417–423. doi:10.3345/kjp.2013.56.10.417
39. Fernández-Alonso AM, Dionis-Sánchez EC, Chedraui P, González-Salmerón MD, Pérez-López FR. First-trimester maternal serum 25-hydroxyvitamin D3 status and pregnancy outcome. *Int J Gynecol Obstet*. 2012;116(1):6–9. doi:10.1016/j.ijgo.2011.07.029
40. Oh C, Keats EC, Bhutta ZA. Effects of vitamin and mineral supplementation during pregnancy on maternal, birth, child health and development outcomes in low- and middle-income countries: a systematic review. *Nutrients*. 2021;12(491):1–13. doi:10.3390/nu12020491
41. Bhutta ZA, Das JK, Rizvi A, et al. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? *Lancet*. 2013;382(9890):452–477. doi:10.1016/S0140-6736(13)60996-4
42. Chakhtoura M, Nassar A, Arabi A, et al. Effect of vitamin D replacement on maternal and neonatal outcomes: a randomised controlled trial in pregnant women with hypovitaminosis D. A protocol. *BMJ Open*. 2016;6(3):e010818. doi:10.1136/bmjopen-2015-010818
43. Whitehouse AJO, Holt BJ, Serralha M, Holt PG, Kusel MMH, Hart PH. Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. *Pediatrics*. 2012;129(3):485–493. doi:10.1542/peds.2011-2644
44. Pérez-López FR, Pasupuleti V, Mezones-Holguin E, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril*. 2015;103(5):1278–1288.e4. doi:10.1016/j.fertnstert.2015.02.019
45. Mojibian M, Soheilykhah S, Zadeh MAF, Moghadam MJ. The effects of vitamin D supplementation on maternal and neonatal outcome: a randomized clinical trial. *Int J Reprod Biomed*. 2015;13(11):687–696.
46. Kovacs CS. Bone metabolism in the fetus and neonate. *Pediatr Nephrol*. 2014;29(5):793–803. doi:10.1007/s00467-013-2461-4
47. Gladys Apriluana SF. Analysis of risk of stunting among children 0–59 months in developing countries and Southeast Asia. *Media Penelit Dan Pengemb Kesehatan*. 2018;8(4):247–256. doi:10.22435/mpk.v28i4.472
48. Roth DE, Morris SK, Zlotkin S, et al. Vitamin D supplementation in pregnancy and lactation to promote infant growth daniel. *J Med Ed Enhanc*. 2017; 1–33. doi:10.1056/NEJMoal800927
49. Bikle DD. Vitamin D: newer concepts of its metabolism and function at the basic and clinical level. *J Endocr Soc*. 2020;4(2):1–20. doi:10.1210/jendso/bvz038