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Vitamin D supplement in pregnancy - dose and recommendations: a systematic review

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ABSTRACT

Objective. This systematic review synthesises evidence from randomised controlled trials (RCTs) on the safety, efficacy, and optimal dosing of vitamin D supplementation during pregnancy.

Materials and Methods. The present study is an integrative review of literature based on clinical trials published in journals indexed in the PubMed databases and the Cochrane Library. A comprehensive search was conducted in PubMed and the Cochrane Library until May 2024. We included RCTs evaluating vitamin D supplementation in pregnant women, focusing on maternal and neonatal outcomes and dosing strategies. A total of 64 RCTs were thematically synthesised using PRISMA guidelines.

Results. Evidence from 64 RCTs indicates that vitamin D supplementation is associated with improved maternal 25(OH) D levels, especially when administered at daily doses of ≥ 2,000 IU. Supplementation of 4,000 IU/day was found to be safe and most effective in achieving maternal and neonatal sufficiency. Higher intermittent doses (*e.g.*, 50,000 IU every two weeks) also showed safety and improved metabolic profiles in some populations. While supplementation did not consistently reduce preeclampsia or gestational diabetes mellitus, it was associated with a lower risk of atopic eczema in offspring during the first year of life and improved bone mineralisation in children up to six years of age.

Conclusions. Vitamin D supplementation during pregnancy is safe and effective in correcting deficiency, particularly at doses ≥ 2,000 IU/day. Although clinical benefits on major obstetric outcomes remain inconsistent, supplementation may offer advantages in select populations. Defining baseline vitamin D status, ethnicity, and timing of supplementation remains crucial when determining optimal dosing strategies.

INTRODUCTION

Vitamin D: physiology and source

Vitamin D is a fat-soluble, lipophilic prohormone proven to have many metabolic and biological functions. This vitamin comes primarily from exposure to sunlight and is found naturally only in a few foods, such as fish-liver oils, fatty fish, mushrooms, egg yolks, butter, and liver. There are two physiologically active forms of vitamin D collectively called calcife-

rol: D2 (ergocalciferol) and D3 (cholecalciferol). Plants synthesise vitamin D2 while vitamin D3 is produced in humans upon skin exposure to ultraviolet light B (UVB) radiation [1, 2]. The foetus is entirely dependent on maternal sources of vitamin D [2, 3].

Importance of vitamin D

The classical role of vitamin D is in calcium and phosphate homeostasis, which is required for bone mineralisation [4, 5]. However, vitamin D is a crucial modulator of many essential biological effects. The actions of vitamin D metabolites are mediated by the vitamin D receptor (VDR), which is expressed in most tissues. The VDR has been shown to regulate cellular differentiation and target gene expression in many cell types, including the immune system [5, 6].

Vitamin D in pregnancy: effect on pregnancy outcome and recommendations for its use

In pregnancy, maternal vitamin D status has been linked to many health outcomes in the mother and offspring. During pregnancy, there are significant alterations in phosphate and calcium metabolism owing to calcium accumulating in the foetal skeleton, and as the foetus relies exclusively on the maternal supply of vitamin D, which it receives across the placenta, a low level of vitamin D during the pregnancy and especially during the early stage of pregnancy produce less bone mineral content in the foetal skeleton [2]. A wealth of studies has reported on other obstetric outcomes and complications, including preeclampsia, gestational diabetes, and mode and timing of delivery. Also, many foetal and childhood outcomes are linked to maternal vitamin D status, including measures of foetal size, and later childhood outcomes, such as asthma [4]. As a result, several national and international guidelines recommend vitamin D supplementation during pregnancy. Most recommend 10-15 micrograms (400-600 IU) of vitamin D daily throughout pregnancy, although this is not currently supported by the World Health Organisation (WHO) [1]. The Food and Nutrition Board at the Institute of Medicine of the National Academies suggests that the recommended dietary allowance (RDA) of vitamin D in pregnancy and lactation is 15 micrograms (600 IU), with an estimated average requirement (EAR) of 10 micrograms (400 IU) and tolerable upper intake level of 100 micrograms (4,000 IU). The Endocrine Society recommends empiric vitamin D supplementation in dosages ranging from 15-125 micrograms (600-5,000 IU) daily for a healthy individual during pregnancy [5, 6].

Vitamin D deficiency: impact of the problem

Vitamin D deficiency is a major public health concern, is widespread among the general population, and pregnant women are a special important group. During pregnancy, the mother's nutrition intake needs to meet both their own nutritional needs and the needs of their developing foetus that is why vitamin D deficiency is highly prevalent in pregnant women; it is found in 60-80% of pregnant women with the highest deficiencies seen in the Middle East [7-9]. Given the high rates of vitamin D deficiency among pregnant women and possible effects on obstetric and offspring outcomes, a review of articles on using vitamin D supplementation in pregnancy was conducted to help inform future practice guidelines. Even though previous systematic reviews have reported on the role of prenatal vitamin D in birth outcomes, the clear evidence for its recommendation and the dose required is poorly understood. The primary purpose of this review is to map the evidence on the effects of vitamin D supplementation on pregnancy outcomes and the preferred dosage used in pregnancy to provide us with a comprehensive understanding of this issue.

MATERIALS AND METHODS

Literature search

The present study is a systematic review based on clinical trials published in journals indexed in the PubMed database and Cochrane Library. The goal strategy of the search was to identify studies that reported the associations between vitamin D supplementation in pregnancy and different aspects of pregnancy outcomes. The basic research strategy was developed for PubMed and modified as required for the Cochrane Library. A literature search was conducted using the following keywords: (((vitamin D) AND (supplement) AND (pregnancy)) AND (outcome). Filters were applied to free full-text and clinical trials.

We searched these databases for eligible articles for inclusion from inception until May 2024; abstracts and unpublished studies were not included. We included randomised controlled trials (RCTs), which adopted the Patient Intervention Comparison Outcome structure. The articles were selected from the search in the databases, from the reading

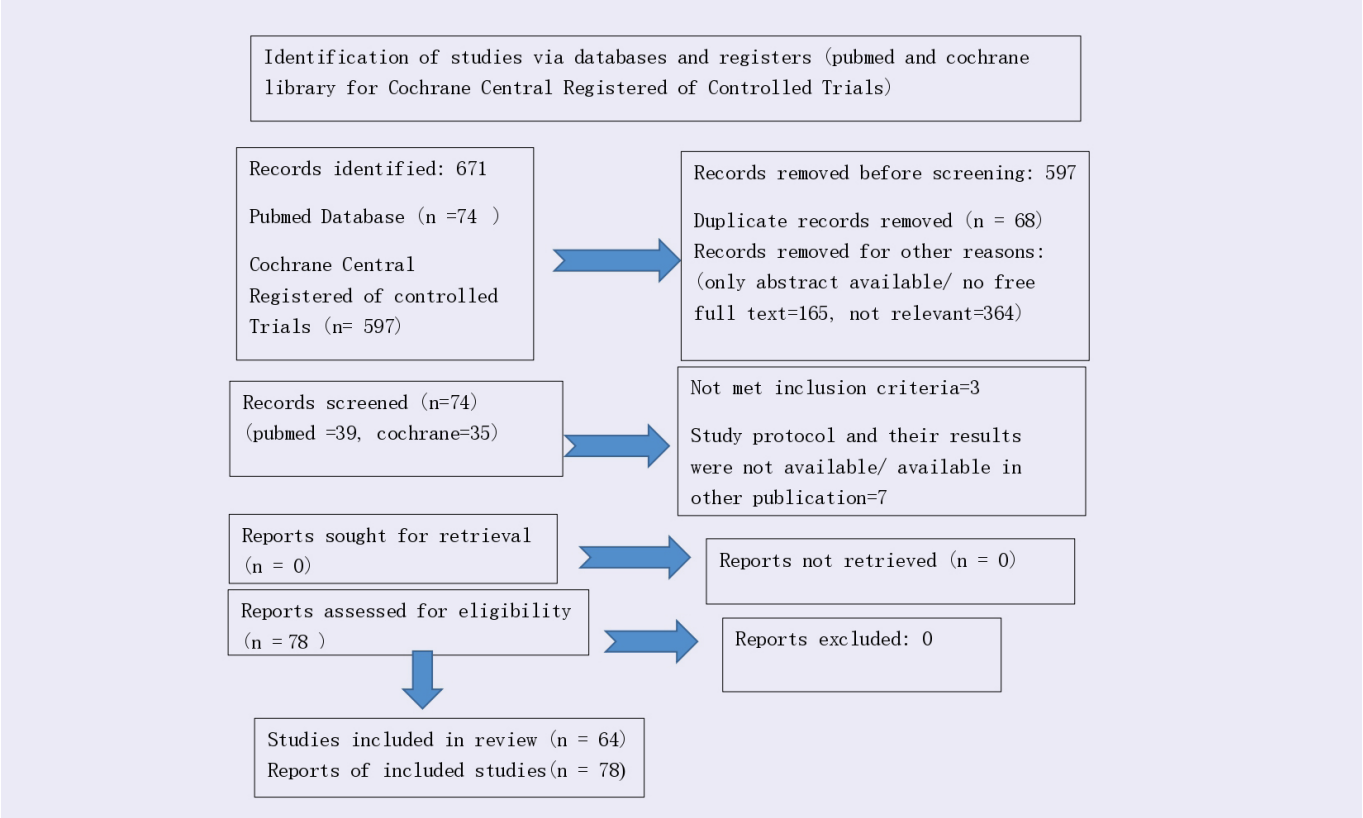

Figure 1. *PRISMA flow diagram.*

and selection of titles and abstracts, to the full selection of articles. The search was limited to human subjects and English language articles. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed.

Inclusion and exclusion criteria

Studies were selected only if they satisfied the following criteria:

1. Original research article
2. Available in English.
3. Study carried out on humans (pregnant women of any gestational age)
4. The exposure of interest is vitamin D supplementation during pregnancy, irrespective of dose, duration, or time of commencement. Eligible intervention groups included daily or single-intermitted vitamin D supplementation (vitamin D2 or D3), alone or in combination with calcium and/or other micronutrients. Control groups included nutrients, no treatment, or a placebo.
5. The main outcomes of interest are the incidence of maternal morbidity and pregnancy outcome, as well as the safety of the dose used.

The exclusion criteria were as follows:

1. Research that did not supplement pregnant women.
2. Observational designs.
3. Review articles, letters to the editor, editorial materials, meeting abstracts, comments, case reports, and editorial notes.
4. Research in non-humans.
5. Studies that could not isolate the effects of vitamin D supplementation or intake.
6. Topics unrelated to the review.

Study selection and data extraction

The included studies were reviewed. One reviewer initially reviewed titles and abstracts. In the first phase, duplicates, trials available as abstract only, and not relevant topics were excluded. An in-depth review of full papers follows this. Then two review authors independently 1) assessed the eligibility of trials against the inclusion criteria, 2(extracted data from included trials, and 3) assessed the risk of bias in the included trials. The detailed steps of the study selection are given as a PRISMA flow diagram in **Figure 1**.

From all the eligible studies, the authors extracted the following information in a standard format: the first author's last name, year of publication, country where the study was performed, descriptions of the study design, number of participants, intervention details, primary outcome of the study, and its report. Pertinent information is summarised in **Table 1**.

Table 1. *Study characteristics.*

Study no.	Author and reference no.	Year of publication.	Country	Type of study	No. of participant.	Information about vitamin D intervention	Aim/Primary outcome	Report
1	Roth (10)	2018	Canada	RCT	1,300	Vitamin D3: (A) 0 IU/week, (B) 4,200 IU/week, (C) 16,800 IU/week, or (D) 28,000 IU/week in pregnancy, all with 0 IU/week postpartum; or (E) 28,000 IU/week in prenatal and postpartum periods	The primary outcome was length-for-age z-score at one year of age according to World Health Organization child growth standards.	*In a population with widespread prenatal vitamin D deficiency and fetal/infant growth restriction, maternal vitamin D supplementation from mid-pregnancy until birth or 6 months postpartum does not influence fetal or infant growth and has no beneficial or harmful effects on numerous other birth and infant outcomes.
2	Bhowmik (11)	2021	Bangladesh	RCT	748	*Oral dose of 200,000 IU of vitamin D every 60- 90 days. *Oral dose of 200 mcg of B12 every 14 days, equivalent to 14 mcg daily.	Evaluation of maternal and delivery outcomes, including adverse outcomes.	*Oral supplementation of high dose intermittent vitamin D or low dose vitamin B12 regime failed to correct the relevant nutritional deficiencies in Bangladeshi pregnant women as per protocol. Both dietary supplementation and high dose vitamin D corrected severe vitamin deficiency. *No significant difference in any of the pregnancy or birth outcomes was observed between three groups.
3	El-Heis (12)	2022	UK	RCT (2°ry analysis)	703	1000 IU vitamin D3/day.	To examine the influence of maternal cholecalciferol supplementation during pregnancy on the risk of atopic eczema in the offspring at ages 12, 24 and 48 months.	Maternal supplementation with cholecalciferol 1,000 IU daily from 14 weeks' gestation to delivery led to a reduced incidence of atopic eczema in the first year of life.
4	Jamilian (13)	2019	Iran	RCT	60	200 IU vitamin D (with other micro-nutrients) twice a day.	To determine the effects of magnesium-zinc-calcium-vitamin D co-supplementation on parameters of inflammation and oxidative stress, and pregnancy outcomes among women with gestational diabetes mellitus (GDM).	*Magnesium-zinc-calcium-vitamin D co-supplementation for 6 weeks to women with GDM may reduce biomarkers of inflammation and oxidative stress.
5	Rodgers (14)	2023	South Carolina	RCT (post hoc analysis)	156	400, 2,000, or 4000 IU vitamin D3/day	To determine whether there is a relationship between 25(OH)D concentration and child neuro development.	*Higher 25(OH)D concentrations early in life and higher doses of maternal vitamin D supplementation during pregnancy may have a positive association with neurodevelopment-al outcomes. *The vitamin D binding protein (VDBP) genotype is associated with neurodevelopment and differentially affects various fields of neurodevelopment.
6	Han (15)	2023	UK, Singapore, and New Zealand	RCT (2°ry analysis)	338	Daily dose of vitamin D3 400 IU (10 mcg) in addition to vitamins B2, B6, B12, as well as zinc, myo-inositol, and probiotics.	To investigate the effects of maternal supplementation from preconception throughout pregnancy until birth on human milk (HM) concentrations of vitamin D3 and B-vitamins.	Maternal supplementation during preconception and pregnancy increased HM vitamin D, but not B-vitamin concentrations in lactation.
7	Mirzakhai (16)	2016	Canada	RCT	876	4,400 vs. 400 IU vitamin D3/day	To assess the effect of vitamin D supplementation (4,400 vs. 400 IU/day), initiated early in pregnancy (10–18 weeks), on the development of preeclampsia.	*Vitamin D supplementation initiated in weeks 10–18 of pregnancy did not reduce preeclampsia incidence in the intention-to-treat paradigm. However, vitamin D levels of 30 ng/ml or higher at trial entry and in late pregnancy were associated with a lower risk of preeclampsia. *Differentially expressed vitamin D–associated transcriptomes implicated the emergence of an early pregnancy, distinctive immune response in women who went on to develop preeclampsia.

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8	Godfrey (17)	2023	UK, Singapore, and New Zealand	RCT (pre-pecified 2°ry analysis)	512	Daily dose of vitamin D3 400 IU (10 µg) in addition to vitamins B2, B6, B12, as well as zinc, myo-inositol, and probiotics.	To determine the influence of vitamin supplementation on longitudinal patterns of maternal vitamin status from preconception, through early and late pregnancy, to 6 months postdelivery.	Preconception and pregnancy supplementation in amounts available in over-the-counter supplements substantially reduced the prevalence of deficiency/ depletion markers before and during pregnancy, and a higher maternal plasma vitamin B12 was maintained during the recommended lactational period.
9	Ku (18)	2023	Singapore	RCT	227	400 IU/ 800 IU vitamin D3 daily.	To investigate whether intervention with an 800 IU oral vitamin D3 supplement compared to a 400 IU of vitamin D3 standard prenatal multivitamin, taken from early pregnancy until delivery, would lead to improved maternal serum 25OHD levels, lipid profiles, and pregnancy outcomes in women with overweight/ obesity (OW/OB) during pregnancy.	800 IU/day of vitamin D3 supplementation effectively increased the 25OHD levels and improved the vitamin D sufficiency status in pregnant women with OW/OB in pregnancy. However, no effect on lipid profiles or pregnancy outcomes were found.
10	Barker (19)	2017	UK	RCT (2°ry analysis)	203	1000 IU vitamin D3/day.	To determine the relationship between self-efficacy, compliance with study protocol and outcome.	*The differences in self-efficacy influence trial outcomes. Such information may help clinicians anticipate responses to routine vitamin D supplementation in pregnancy and identify those who may need more support to comply.
11	Harreiter (20)	2022	UK, Ireland, Austria, Poland, Italy, Spain and Belgium.	RCT (2°ry analysis)	154	1600 IU vitamin D3/day.	To assess the effects of a vitamin D supplementation with 1600 IU Vitamin D3/ day starting in early pregnancy versus placebo on maternal and fetal lipid parameters, body fat distribution as well as pregnancy outcomes.	*Vitamin D supplementation with 1600 IU/day vitamin D3 in overweight/obese pregnant women led to a safe and significant increase of vitamin D levels in pregnancy and high prevalence of vitamin D sufficiency without safety issues. *No significant differences between the treatment arms in maternal lipid parameters nor in fetal lipid parameters or birth outcomes were found.
12	Sudfeld (21)	2022	Tanzania	RCT	2300	3000 IU vitamin D3/ day	The primary outcomes were (i) maternal HIV progression or death, (ii) small for-gestational-age (SGA) live births (<10th percentile), and (iii) infant stunting at 1 year of age (length-for-age z-score <−2).	*Maternal vitamin D3 supplementation during pregnancy and lactation did not significantly affect the risk of maternal HIV disease progression or death, SGA live births, or infant stunting at 1 year of age.
13	Morris (22)	2021	Bangladesh	RCT	1174	4,200, 16,800, and 28 000 IU vitamin D per week.	To examine the effect of maternal vitamin D supplementation during pregnancy and lactation on risk of acute respiratory infection (ARI) in infants up to 6 months of age in Bangladesh.	*Despite a high prevalence of maternal baseline vitamin D deficiency and significant effects of maternal vitamin D supplementation on infant vitamin D status, the intervention did not reduce the risk of microbiologically confirmed ARI in infants up to 6 months of age.
14	Alhomaid (23)	2021	Northen Ireland	RCT	240	10 or 20 µg vitamin D3/ day.	To examine the effects of maternal supplementation of 10 µg compared with 20 µg vitamin D3/ day on maternal and umbilical cord 25(OH) D level.	*Supplementation of 20 µg vitamin D3/d is needed to attain maternal and umbilical cord 25(OH)D concentrations ≥50 nmol/L.
15	Callaghan (24)	2022	Bangladesh	RCT (2°ry analysis)	642	4,200/0, 16,800/0, 28,000/0, or 28,000/28,000 IU vitamin D3/week	To examine hypothesized effects of improvements in early-life vitamin D status on childhood musculoskeletal health.	*Maternal prenatal, with or without postpartum, vitamin D supplementation does not improve child bone mineral content (BMC), areal bone mineral density (aBMD), or grip strength at 4 y of age.

Study no.	Author and reference no.	Year of publication.	Country	Type of study	No. of participant.	Information about vitamin D intervention	Aim/Primary outcome	Report
16	Hornsby (25)	2017	UK	RCT	51	400/ 4,400 IU/day vitamin D3	To investigate the effect on neonatal immunity of maternal supplementation with 4,400 IU/day vitamin D3 during the second and third trimesters of pregnancy.	*Vitamin D supplementation during pregnancy modifies the immune system of the neonate. This modified immune system might be better equipped to protect the host against pathogenic infections.
17	Hollis (26)	2011	South Carolina	RCT	350	400, 2000 or 4000 IU vitamin D3/ day.	Maternal/ neonatal circulating 25(OH)D level at delivery.	*Vitamin D supplementation of 4000 IU/day for pregnant women is safe and most effective in achieving sufficiency in all women and their neonates regardless of race, whereas the current estimated average requirement is comparatively ineffective at achieving adequate circulating 25(OH)D concentrations, especially in African Americans.
18	Goldring (27)	2013	UK	RCT	180	800 IU ergocalciferol daily until delivery or single oral bolus of 200,000 IU cholecalciferol	To examine the effect of prenatal vitamin D on childhood wheezing.	*Prenatal vitamin D supplementation in late pregnancy that had a modest effect on cord blood vitamin D level, was not associated with decreased wheezing in offspring at age three years.
19	Curtis (28)	2021	UK	RCT (2°ry analysis)	372	1000 IU vitamin D3/ day.	The influence of vitamin D supplementation in pregnancy on maternal postnatal bone indices.	*Maternal urinary C-terminal telopeptide of type I collagen (CTX), a bone resorption marker, rises through pregnancy, although to a lesser degree with gestational cholecalciferol supplementation, and is inversely associated with maternal bone mass postpartum.
20	Schulz (29)	2017	South Carolina	RCT	43	400 IU/ 4,400 IU of vitamin D3/ day	To investigate the role of maternal 25(OH)D, the nutritional indicator of vitamin D status, in relation to placental maintenance and, specifically, expression of placental gene targets related to angiogenesis and vitamin D metabolism.	*A significant association between maternal vitamin D status and the expression of Soluble FMS-like tyrosine kinase 1 (sFlt-1) and vascular endothelial growth factor (VEGF) at the mRNA level were reported. Achieving maternal circulation of 25(OH)D 100 nmoles/L suggests the impact of maternal vitamin D3 supplementation on gene transcription in the placenta, thereby potentially decreasing antiangiogenic factors that may contribute to vascular pregnancy complications.
21	Karamali (30)	2016	Iran.	RCT	60	1,000 mg Ca/day and two pearls containing 1,250 µg (50 000 IU) of vitamin D3 during the intervention (one at study baseline and another at day 21 of the intervention)	To assess the effects of Ca + vitamin D supplementation on pregnancy outcomes in women with gestational diabetes mellitus (GDM).	*Ca + vitamin D supplementation for 6 weeks among pregnant women with GDM led to decreased caesarean section rate and maternal hospitalization, and decreased macrosomia, hyperbilirubinaemia and hospitalization in newborns.
22	Rodrigues (31)	2021	Brazil	RCT (feasibility trial)	69	(1) fortified sachet (vitamin D3 (500 IU) and calcium) and powdered milk plus periodontal therapy during pregnancy (early PT); (2) placebo sachet and powdered milk plus early PT; (3) fortified sachet and powdered milk plus late PT (after delivery); (4) placebo sachet and powdered milk plus late PT.	To explore the effect of a non-pharmaceutical multi-component intervention on periodontal health and metabolic and inflammatory profiles among pregnant women with periodontitis receiving prenatal care in a Brazilian public health centre.	*The mean BOP (% sites with bleeding on probing) was significantly reduced in the early PT groups, while BOP worsened in the late PT groups. No significant effect of fortification on BOP was observed. Changes in glucose levels and variation on birthweight did not differ among groups
23	Cooper (32)	2016	UK	RCT (2°ry analysis)	737	1,000 IU vitamin D3/ day	Body bone mineral content (BMC) of the neonate.	*Supplementation of mothers with 1,000 IU/day cholecalciferol during pregnancy did not lead to increased offspring whole body BMC compared with placebo.

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24	Braithwaite (33)	2019	UK	RCT (2°ry analysis)	195	Vitamin D3 1000 IU/ day from ~14 weeks gestation.	To identify whether antenatal vitamin D3 supplementation affects iron status (via hepcidin suppression) and/or inflammation.	*Vitamin D3 supplementation had no effect on hepcidin, ferritin, or inflammatory status suggesting no adjunctive value of vitamin D3 in reducing rates of antenatal iron deficiency.
25	Moon (34)	2016	UK	RCT	829	1,000 IU vitamin D3/ day.	To assess which maternal and environmental characteristics were associated with better 25(OH)D level following vitamin D supplementation.	*Women who gain more weight during pregnancy, have lower 25(OH)D in early pregnancy, or deliver in winter tend to achieve a lower 25(OH)D in late pregnancy when supplemented with 1,000-IU/day cholecalciferol than do women with the converse attributes.
26	Motamed (35)	2019	Iran	RCT	84	1000 / 2000 IU vitamin D/day.	To evaluate the efficacy of two doses of vitamin D3 supplementation during pregnancy on maternal and cord blood vitamin D status, inflammatory biomarkers, and maternal and neonatal outcomes.	*Supplementation with 2,000 IU/day vitamin D3 instead of 1000 IU/day from the first trimester of pregnancy could be more effective in improving vitamin D status of the pregnant women and decreasing pro-inflammatory cytokines including TNF-α in mother and IL-6 in cord blood. *Also supplementation with 2000 IU/day vitamin D3 helps improve neonatal outcomes including the birth sizes (weight, length, and head circumference) compared with 1000 IU/day group.
27	Kabuyanga (36)	2024	Democratic Republic of Congo	RCT	1,159	A single monthly dose of vitamin D3 (60,000 IU) orally for 6 months.	To evaluate the effect of cholecalciferol supplementation on the incidence of preeclampsia in primigravid women and its related maternal and foetal outcomes.	*A single monthly dose (60,000 IU) of vitamin D supplementation, started in early pregnancy, significantly reduced the incidence of preeclampsia and its maternal and foetal complications.
28	Litonjua (37)	2020	USA	RCT (2°ry analysis) VDAART	806	4400 IU of vitamin D3 per day	To determine whether children born to mothers who had received 4400 IU of vitamin D3/ day during pregnancy (vitamin D group) would have a lower incidence of asthma and recurrent wheeze at the age of 6 years.	*Vitamin D supplementation during the prenatal period alone did not influence the 6-year incidence of asthma and recurrent wheeze among children who were at risk for asthma.
29	Enkhmaa (38)	2018	Mongolia	RCT	344	600, 2,000, or 4,000 IU vitamin D3	To test the impact of different concentrations of vitamin D supplementation on 25(OH)D concentrations of pregnant women in Mongolia.	*Daily supplementation of 4000 IU during pregnancy is safe and achieved higher maternal and neonatal 25(OH)D concentrations than 2000 IU. Daily 600 IU supplements are insufficient to prevent vitamin D deficiency in Mongolia.
30	Vaziri (39)	2016	Iran	RCT	136	2,000 IU vitamin D3/ day.	To evaluate the effect of vitamin D3 supplementation on perinatal depression scores.	*Consuming 2,000 IU vitamin D3 daily during late pregnancy was effective in decreasing perinatal depression levels.
31	Moon (40)	2017	UK	RCT	682	1,000 IU/ day vitamin D3 from 14 weeks of gestation until delivery.	To determine whether single-nucleotide polymorphisms (SNPs) in DHCR7, CYP2R1, CYP24A1, and GC genes are associated with the response to gestational cholecalciferol supplementation.	*Common genetic variation is associated with baseline 25(OH)D in pregnancy and the response to antenatal supplementation with 1,000 IU/day cholecalciferol, but with differing SNPs appearing to be important before and after supplementation. (Our findings suggest that analysis of SNPs may have an important role in identifying high-risk categories of individuals who are likely to require higher doses of vitamin D to achieve repletion).
32	Wagner (41)	2013	South Carolina	RCT	161	400, 2,000, or 4000 IU vitamin D3/ day	To determine whether 4,000 IU vitamin D3/ day (vs. 2,000 IU/day) during pregnancy is safe and improves maternal/neonatal 25(OH)D in a dose-dependent manner.	*Maternal supplementation with 2,000 and 4,000 IU vitamin D/day during pregnancy improved maternal/neonatal vitamin D status. *Evidence of risk reduction in infection, preterm labor and preterm birth was suggestive, requiring additional studies powered for these endpoints.

Study no.	Author and reference no.	Year of publication.	Country	Type of study	No. of participant.	Information about vitamin D intervention	Aim/Primary outcome	Report
33	Litonjua (42)	2016	USA	RCT	806	daily 4,000 IU vitamin D plus a prenatal vitamin containing 400 IU vitamin D/a placebo plus a prenatal vitamin containing 400 IU vitamin D.	To determine whether prenatal vitamin D supplementation can prevent asthma or recurrent wheeze in early childhood.	*In pregnant women at risk of having a child with asthma, supplementation with 4,400 IU/day of vitamin D compared with 400 IU/day significantly increased vitamin D levels in the women. *The incidence of asthma and recurrent wheezing in their children at age 3 years was lower by 6.1%, but this did not meet statistical significance; however, the study may have been underpowered.
34	Zerofsky 43))	2016	California	RCT	51	400/ 2000 IU vitamin D3/ day from < 20 week to delivery	To assess the effects of vitamin D supplementation during pregnancy on vitamin D status and markers of immune function associated with adverse pregnancy outcomes.	*Supplementation with 2000 IU/day is more effective at increasing vitamin D status in pregnant women than 400 IU/day and is associated with increased regulatory T cell immunity that may prevent adverse outcomes caused by excess inflammation.
35	Roth (44)	2012	Bangladesh	RCT	61	A single oral vitamin D3 dose (70,000 IU)	To assess the change in serum 25-hydroxyvitamin D concentration over time, estimated using model-independent pharmacokinetic parameters.	*The response to a single 70,000 IU dose of vitamin D3 was similar in pregnant and non-pregnant women in Dhaka and consistent with previous studies in non-pregnant adults. These preliminary data support the further investigation of antenatal vitamin D3 regimens involving doses of ≤70,000 IU in regions where maternal-infant vitamin D deficiency is common.
36	Roth (45)	2013	Bangladesh	RCT	160	35,000 IU/week of vitamin D3	To evaluate the effect of high-dose prenatal 3rd trimester vitamin D3 supplementation on maternal and neonatal (cord blood) serum (25(OH)D) concentration (primary biochemical efficacy outcome) and maternal serum calcium concentration (primary safety measure).	*Antenatal 3rd-trimester vitamin D3 supplementation (35,000 IU/week) significantly raised maternal and cord serum 25(OH)D concentrations above 50 nmol/L in almost all participants without inducing hypercalcemia or other observed safety concerns. *Doses up to 35,000 IU/week may be cautiously used in further research aimed at establishing the clinical effects and safety of vitamin D3 supplementation in pregnancy.
37	Roth (46)	2013	Bangladesh	RCT	28	70,000 IU once + 35,000 IU/week vitamin D3 or 14,000 IU/week vitamin D3	To assess the biochemical dose-response and tolerability of high-dose prenatal vitamin D3 supplementation.	*A regimen of an initial dose of 70,000 IU and 35,000 IU/week vitamin D3 in the third trimester of pregnancy was non-hypercalcemic and attained [25(OH)D] ≥ 80 nmol/L in virtually all mothers and newborns.
38	Newton (47)	2022	South Carolina.	RCT	74	400 IU/ 6400 IU vitamin D3/day	To determine the effects of maternal vitamin D sufficiency on infant plasma concentrations of (25(OH)D) and 11 cytokines.	*Maintenance of maternal vitamin D sufficiency during pregnancy likely continues to affect the health of breastfed infants.
39	Han (48)	2023	Southampton-on (UK), Singapore, and Auckland (New Zealand).	RCT	338	Daily dose of vitamin D3 400 IU (10 µg) in addition to vitamins B2, B6, B12, as well as zinc, myo-inositol, and probiotics.	To investigate the effects of maternal supplementation from preconception throughout pregnancy until birth on human milk (HM) concentrations of vitamin D3 and B-vitamins and to characterise longitudinal changes in milk concentrations of these vitamins.	*Maternal supplementation during preconception and pregnancy increased HM vitamin D, but not B-vitamin concentrations in lactation.
40	Wagner (49)	2013	South Carolina	RCT	504	400, 2000, or 4000 IU vitamin D3/day / 2000 or 4000 IU vitamin D3/day.	To assess the safety and health effects of vitamin D supplementation during pregnancy.	*Supplementation with 4,000 IU/day was associated with lower risk of hypovitaminosis D than Control and 2,000 IU groups. *While not statistically significant, there was a trend toward lower rates of comorbidity of pregnancy as supplementation dose increased

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41	Dawodu (50)	2013	UAE	RCT	162	400, 2000, and 4000 IU/day vitamin D3	To determine effectiveness and safety of prenatal 2000 IU and 4000 IU/day compared with 400 IU/day vitamin D3 supplementation in population in which vitamin D deficiency is endemic.	*Vitamin D supplementation of 2000 and 4000 IU/day appeared safe in pregnancy, and 4000 IU/day was most effective in optimizing serum 25(OH)D concentrations in mothers and their infants.
42	Harrington (51)	2014	Bangladesh	RCT	130	35,000 IU/week vitamin D3 from 26 to 29 wk of gestation.	To assess the effect of high-dose antenatal vitamin D supplementation on fetal and neonatal calcium concentrations.	*High-dose antenatal third-trimester vitamin D supplementation attenuated the early postnatal calcium nadir, without increasing the risk of postnatal hypercalcemia.
43	Hossain (52)	2014	Pakistan	RCT	193	4,000 IU vitamin D3 daily, started at 20 weeks and continued till delivery.	To determine whether vitamin D supplementation during pregnancy affects obstetric and neonatal outcomes.	*Maternal vitamin D supplementation improved maternal and neonatal vitamin D status. *The obstetric outcomes were comparable between the two groups. *One- and 5-minute Apgar scores were significantly higher in the intervention group Neonatal anthropometric parameters were comparable between the two groups.
44	Karamali (53)	2015	Iran	RCT	60	50 000 IU vitamin D3 every 2 weeks from 20 to 32 weeks of gestation.	To assess the beneficial effects of high-dose vitamin D supplementation on metabolic profiles and pregnancy outcomes among pregnant women at risk for pre-eclampsia.	*High-dose vitamin D administration among women at risk for pre-eclampsia had beneficial effects on insulin metabolism parameters, serum HDL-cholesterol, and plasma total antioxidant capacity concentrations, but did not affect fasting plasma glucose, other lipid profiles, inflammatory factors and other biomarkers of oxidative stress. *No significant effect of high-dose cholecalciferol supplementation on pregnancy outcome.
45	Asemi (54)	2015	Iran	RCT	45	50 000 IU vitamin D3 2 times during the study: at study baseline and day 21 of intervention.	To assess the effect of vitamin D supplementation on pregnancy outcomes of pregnant women with gestational diabetes mellitus (GDM) who were not on oral hypoglycemic agents.	*Vitamin D supplementation for 6 weeks among pregnant women with GDM resulted in decreased maternal polyhydramnios and infant hyperbilirubinemia compared with placebo.
46	Griffiths (55)	2015	UK	RCT	99	800 IU ergocalciferol daily until delivery, or a single oral bolus of 200,000 IU cholecalciferol	To examine the effect of prenatal Vitamin D on healthcare utilisation in the first three years of life.	* There is no evidence that prenatal vitamin D supplementation from 27 weeks gestation to delivery, at doses which failed to completely correct maternal vitamin D deficiency, influence overall healthcare utilisation in children in the first 3 year.
47	Singh (56)	2021	India	RCT	164	60,000 IU vitamin D3 oral tablet/ capsule weekly / 60,000 IU vitamin D3 injection intramuscular every fortnight for 8 weeks.	To study perinatal outcomes in vitamin D deficiency, and effect of oral and intramuscular vitamin D3 supplementation in antenatal women on pregnancy outcomes.	*There is a high prevalence of vitamin D deficiency in pregnant women in India. Supplementation of Vitamin D as a part of routine antenatal care needs to be established. *Both oral and intramuscular vitamin D are effective.
48	Stoutjesdijk (57)	2019	Netherlands	RCT	36	Increasing dose of daily vitamin D3 (10, 35, 60 and 85 µg) from 20 weeks gestation up to 4 weeks postpartum (PP).	To study the influence of daily 10–85 µg vitamin D supplements during pregnancy and lactation on maternal vitamin D status and mature milk antirachitic activity (ARA).	*Dosages of 35 µg vitamin D3/day or higher were needed to increase 25(OH)D to adequacy in >97·5% of participants at 36 weeks gestation, while >85 µg/d was needed to reach this target in >97·5% of participants at 4 weeks PP. *Milk ARA at 4 weeks PP increased in a dose-dependent manner.
49	Rostami (58)	2018	Iran	RCT	788	50,000 IU vitamin D3 oral weekly/ 300,000 IU vitamin D3 intramuscularly.	To determine the effectiveness of a prenatal screening program on optimizing [25(OH)D] levels and preventing pregnancy complications.	*A prenatal vitamin D screening and treatment program is an effective approach in detecting deficient women, improving 25(OH)D levels, and decreasing pregnancy adverse outcomes.

Study no.	Author and reference no.	Year of publication.	Country	Type of study	No. of participant.	Information about vitamin D intervention	Aim/Primary outcome	Report
50	Yap (59)	2015	Sydney	RCT	158	5,000 IU vitamin D3 daily/ 400 IU vitamin D3 daily	To investigate the effects of vitamin D supplementation on glucose metabolism during pregnancy.	*High dose vitamin D supplementation commencing at a mean of 14 weeks' gestation does not improve glucose levels in pregnancy. However, in women with baseline levels <32 ng/mL, 5,000 IU per day was well tolerated and highly effective at preventing neonatal vitamin D deficiency.
51	Mir (60)	2016	India	RCT	87	1,000 IU Vitamin D daily/ 30,000 IU Vitamin D monthly/2,000 IU Vitamin D daily/60,000 IU Vitamin D monthly.	To assess the efficacy and safety of various doses of vitamin D supplementation during pregnancy	Vitamin D supplementation with 2000 IU/day or 60,000 IU/month is very effective and safe in achieving Vitamin D sufficiency in pregnant women.
52	Wolsk (61)	2017	USA, Denmark	RCT		4,000 IU vitamin D3/day/2,400 IU vitamin D3/day.	To perform a combined analysis of two randomized controlled trials and investigate whether maternal (25(OH)D) level at trial entry modified the risk of asthma/recurrent wheeze from 0-3 years.	*The combined analysis shows that vitamin D supplementation during pregnancy results in a significant reduced risk of asthma/recurrent wheeze in the offspring, especially among women with 25(OH)D level 30 ng/ml at randomization, where the risk was almost halved.
53	Chawes (62)	2016	Denmark	RCT	581	Vitamin D3 (2,400 IU/day) from 24 weeks gestation to 1 week postpartum.	To determine whether supplementation of vitamin D3 during the third trimester of pregnancy reduces the risk of persistent wheeze in the offspring.	*The use of 2,800 IU/day of vitamin D3 during the third trimester of pregnancy compared with 400 IU/day did not result in a statistically significant reduced risk of persistent wheeze in the offspring through age 3 years. However, interpretation of the study is limited by a wide confidence interval (CI) that includes a clinically important protective effect.
54	Mirzaei-Azandaryanl (63)	2022	Iran	RCT	84	4,000 IU vitamin D3 daily.	To determine the effect of vitamin D supplementation on fasting blood glucose (FBG) levels, fasting blood insulin (FBI) levels and insulin resistance index (HOMA-IR) (primary outcomes) and symptoms of depression, musculoskeletal pain, frequency of gestational diabetes (GDM) and the frequency of abortion (secondary outcomes).	*Vitamin D could improve the musculoskeletal pain in pregnant women but couldn't decrease FBG, FBI, HOMA-IR, depression symptoms score, incidence of GDM and abortion.
55	Brustad (64)	2020	Denmark	RCT (2°ry analysis)	517	2800 IU/day (high-dose) vs 400 IU/d (standard-dose) from pregnancy week 24 until 1 week after birth.	To investigate the effect of a high dose vs standard dose of vitamin D supplementation in pregnancy on anthropometric and bone outcomes until age 6 years in the offspring.	*High-dose vitamin D supplementation in pregnancy improved offspring bone mineralization through age 6 years compared with the standard dose, suggesting an increased recommended gestational intake, which may influence peak bone mass, fracture risk, and risk of osteoporosis later in life. We found no supplementation effect on anthropometric outcomes.
56	Mojibian (65)	2015	Iran	RCT	470	400 IU vitamin D daily / 50,000 IU vitamin D every 2 weeks.	To assess the effects of 50,000 IU of vitamin D every two weeks supplementation on the incidence of gestational diabetes (GDM), gestational hypertension, preeclampsia and preterm labor, vitamin D status at term and neonatal outcomes contrasted with pregnant women that received 400 IU vitamin D daily.	*Consumption of 50,000 IU vitamin D every 2 weeks from 12 weeks of pregnancy until delivery significantly reduced the incidence of GDM.
57	Asemi (66)	2012	Iran	RCT	49	500 mg carbonate calcium plus 200 IU vitamin D3.	To determine the effects of consumption calcium-vitamin D supplements on metabolic profiles among Iranian pregnant women at risk for pre-eclampsia.	*Consumption of calcium-vitamin D supplements for 9 weeks during pregnancy among pregnant women at risk for pre-eclampsia resulted in decreased fasting plasma glucose (FPG) and serum triglycerides levels as compared to the placebo group, but could not affect serum total-, HDL-, LDL-cholesterol levels

Study no.	Author and reference no.	Year of publication.	Country	Type of study	No. of participant.	Information about vitamin D intervention	Aim/Primary outcome	Report
58	Sass (67)	2020	Denmark	RCT (2°ry analysis)	551	High-dose (i.e, 2800 IU/day) vs standard dose (i.e, 400 IU/day) vitamin D3 supplementation from pregnancy week 24 until 1 week after birth.	To determine whether high-dose vitamin D supplementation during pregnancy improves offspring neurodevelopment from birth to age 6 years.	*Maternal high dose vitamin D supplementation during the third trimester of pregnancy did not improve neurodevelopmental outcomes in the offspring during the first 6 years of life.
59	Motamed (68)	2020	Iran	RCT (2°ry analysis)	73	1,000 IU/2,000 IU/ day vitamin D.	To assess the efficacy of two dosages of vitamin D (1000 IU/day and 2000 IU/day) on certain metabolic parameters including glycaemic, lipidemic and parathyroid hormone as well as oxidative stress (OS) status.	*Supplementation with 2,000 IU/d vitamin D had no more beneficial effects on the studied biomarkers of glycemic, lipidemic and OS status of the maternal and cord blood than with 1,000 IU/day. Nevertheless, supplementation with 2,000 IU a day, compared with 1,000 IU/day, was more effective in improving vitamin D status and lowering the occurrence of suboptimal circulating calcidiol concentrations during pregnancy.
60	Nausheen (69)	2021	Pakistan	RCT	257	4,000 IU/day/ 2,000 IU/ day/ 400 IU/ day vitamin D3.	To evaluate the effect of different doses of vitamin D supplementation during pregnancy on biochemical markers (serum 25(OH)D, calcium, phosphorus and alkaline phosphatase) in women and neonates, and on pregnancy and birth outcomes (gestational diabetes, pre-eclampsia, low birth weight, preterm births and stillbirths).	*Vitamin D supplementation of 4,000 IU/day was more effective in reducing vitamin D deficiency among pregnant women and improving serum 25(OH)D levels in mothers and their neonates compared with 2,000 IU/day and 400 IU/day.
61	Nørrisgaard (70)	2019	Danemark	RCT (Post hoc analysis)	496	2,400 IU/day vitamin D3.	To assess the association of a high-dose vitamin D supplementation in pregnant women with enamel defects and caries in their offspring.	*High-dose vitamin D supplementation during pregnancy was associated with approximately 50% reduced odds of enamel defects in the offspring.
62	Valizadeh (71)	2016	Iran	RCT	84	200,000 IU vitamin D3 for each of the first two days, and then 50,000 IU per week thereafter, up to 700,000 IU in total.	To assess the impact of prenatal vitamin D supplementation on postpartum dysglycaemia in gestational diabetes mellitus (GDM) patients.	*Although the high vitamin D supplementation dose safely increases the serum 25OHD, in GDM cases, the higher dose does not affect the plasma glucose level or insulin resistance at short term follow-up after delivery.
63	Naghshineh (72)	2016	Iran	RCT	138	600 IU vitamin D daily at 16 week gestation until labor.	To investigate the association between vitamin D supplement and preeclampsia in pregnant women.	* Vitamin D supplementation during the third trimester of pregnancy; reduce the risk of preeclampsia however, this was not statistically significant.
64	Etemadifar (73)	2015	Iran	RCT	15	50,000 IU/week vitamin D3.	To assess the safety and efficacy of high-dose oral vitamin D3 supplementation during pregnancy in women with multiple sclerosis (MS) in Isfahan, Iran.	*Adding high dose vitamin D3 supplementation during pregnancy to routine care of women with MS had significant effect on the serum 25(OH)D levels, expanded disability status scale (EDSS) and number of relapse events during pregnancy and within 6 months after delivery.

Table 2. *Summary of dose–response categories of the studies included.*

Outcome Domain	Dose Group	No. of RCTs	Effect Observed	Representative Studies
Maternal 25(OH)D levels post-supplementation	<1,000 IU/day	~6	Often insufficient to correct the deficiency	Alhomaid (2021), Ku (2023), Moon (2016), Stoutjesdijk (2019), Dawodu (2013), Nausheen (2021)
Maternal 25(OH)D levels post-supplementation	1,000–2,000 IU/day	~7	Moderate efficacy; improves status in non-deficient women	Motamed (2019), Enkhmaa (2018), Mir (2016), Godfrey (2023), Harreiter (2022), Vaziri (2016), Wagner (2013)
Maternal 25(OH)D levels post-supplementation	>2,000 IU/day	~9	Most effective in correcting deficiency; consistently raised maternal and neonatal levels	Roth (2018, 2013), Hollis (2011), Dawodu (2013), Nausheen (2021), Enkhmaa (2018), Wagner (2013), Mirzakhani (2016), Kabuyanga (2024),
Maternal 25(OH)D levels post-supplementation	Bolus doses (e.g., ≥50,000 IU every 2 weeks or monthly)	~5	Showed safety and improved vitamin D status, but requires more study	Mojibian (2015), Singh (2021), Rostami (2018), Naghshineh (2016), Yap (2015)

We also noted limitations and possible bias, such as small samples, suboptimal exposure, outcome measures, or other indications of poor study quality (for example, inadequate consideration of confounders).

RESULTS

Overview of included studies

A total of 64 randomised controlled trials (RCTs) were included in this systematic review. These studies were published between 2011 and 2024 and were conducted across diverse geographic regions, including North America, Europe, South Asia, the Middle East, and Sub-Saharan Africa. Intervention doses ranged from 400 IU/day to 50,000 IU every two weeks, with some studies using bolus dosing strategies. Outcomes assessed included maternal vitamin D status, metabolic parameters, neonatal outcomes, immune function, bone health, and long-term child development. The important methodological features and baseline characteristics of the included trials are summarised in **Table 1**.

Key findings by outcome domain

Maternal vitamin D status

Most studies showed a dose-dependent increase in maternal serum 25(OH) D levels, though optimal dosing varied across populations:

- Supplementation with ≥ 2,000 IU/day was consistently associated with achieving maternal sufficiency (≥ 30 ng/mL), particularly in baseline-deficient populations (*e.g.*, Motamed [35], Enkhmaa [38], Wagner [49]).
- Lower doses (< 1,000 IU/day) often failed to correct deficiency (*e.g.*, Alhomaid [23], Stoutjesdijk [57]).
- Daily doses of 4,000-5,000 IU/day were found to be the most effective in correcting severe deficiency and maintaining adequate levels throughout pregnancy (Roth [45], Hollis [26], Nausheen [69]).

Table 2 summarises the included studies' dose-response categories.

Preeclampsia

Evidence remains mixed regarding the effect of vitamin D supplementation on the incidence of preeclampsia:

- Kabuyanga *et al.* [36] reported a significant reduction in preeclampsia risk with monthly 60,000 IU vitamin D3.
- In contrast, Mirzakhani *et al.* [16] found no significant difference in preeclampsia rates between women receiving 4,400 IU/day *vs* 400 IU/day.
- Subgroup analyses suggest that achieving a 25(OH) D level > 30 ng/mL may be more important than dose alone (Mirzakhani [16], Schulz [29]).

Gestational Diabetes Mellitus (GDM)

Some trials showed beneficial effects of vitamin D on glucose metabolism, while others did not:

- Asemi *et al.* [54] found reduced polyhydramnios and neonatal hyperbilirubinemia with supplementation among GDM patients.
- Yap *et al.* [59] observed no improvement in glucose metabolism despite increased vitamin D levels.
- Mojibian *et al.* [65] found that 50,000 IU vitamin D every 2 weeks significantly reduced the incidence of GDM.
- Overall, there is limited evidence to support routine high-dose vitamin D as a preventive strategy for GDM.

Certain Maternal Illnesses (HIV, Multiple Sclerosis, Perinatal Depression)

Few trials focused on the impact of vitamin D supplementation on specific maternal conditions:

- Regarding perinatal depression, Vaziri *et al.* (2016) found that 2,000 IU/day of vitamin D3 during late pregnancy was effective in decreasing depression scores among pregnant women [39].
- For HIV, Sudfeld *et al.* (2022) found no significant effect of 3,000 IU/day of vitamin D3 on maternal disease progression or infant outcomes such as small-for-gestational age birth or stunting at one year [21].
- Concerning multiple sclerosis (MS), Etemadifar *et al.* (2015) reported that high-dose vitamin D3 supplementation (50,000 IU/week) improved disability scores and decreased relapse rates in pregnant women with MS [73].

While only a few trials addressed these conditions, the available data suggest that vitamin D supplementation may offer some benefit, particularly in populations with severe deficiency or pre-existing conditions.

Maternal bone health

One trial specifically examined the impact of vitamin D supplementation on maternal postnatal bone indices [28]. The study reported that 1,000 IU/day of vitamin D3 during pregnancy was associated with lower postpartum bone resorption markers, suggesting a beneficial effect on maternal bone metabolism.

Additionally, urinary CTX, a marker of bone resorption, was inversely related to postpartum bone mass, indicating that maintaining adequate vitamin D status during pregnancy may help preserve maternal skeletal integrity.

These findings support the hypothesis that vitamin D supplementation may contribute to maternal bone health, although more robust and long-term studies are required.

Neonatal and child outcomes

High-dose vitamin D supplementation (> 2,000 IU/day) improved neonatal vitamin D status but had inconsistent effects on clinical outcomes:

- Brustad *et al*. [64] found improved bone mineralisation at age 6 years with high-dose supplementation.
- El-Heis *et al*. [12] observed a reduced incidence of atopic eczema in the first year of life among infants whose mothers received 1,000 IU/day of vitamin D3 from 14 weeks' gestation to delivery.
- Litonjua *et al*. [37, 42] reported no significant impact on childhood asthma or wheezing.
- Evidence suggests supplementation improves cord blood vitamin D levels, but long-term benefits remain uncertain.

Immune and neurodevelopmental effects

Emerging evidence suggests potential immunomodulatory and neurodevelopmental benefits:

- Zerofsky *et al.* [43] found that 2,000 IU/day increased regulatory T cell immunity, potentially reducing inflammation-related adverse outcomes.
- Sass *et al.* [67] found no significant improvement in offspring neurodevelopment with high-dose supplementation, though earlier studies like Rodgers *et al.* [14] suggested a positive association with higher early-life 25(OH)D concentrations.

Dosing and safety

Supplementation up to 4,000-5,000 IU/day was generally safe and effective in improving maternal vitamin D status:

- No cases of hypercalcemia or toxicity were reported in trials using ≤ 5,000 IU/day (Roth [45], Hollis [26]).
- Higher bolus doses (*e.g.*, 50,000 IU every 2 weeks) also showed safety but require further study before being widely adopted (Mojibian [65], Singh [56]).

Factors influencing response to supplementation

Baseline vitamin D status significantly influenced response to supplementation:

- Women who were severely deficient at baseline often required higher doses (> 2,000 IU/day) to achieve sufficiency (Alhomaid [23], Moon [34]).
- Maternal weight gain, season of supplementation, and genetic variation (*e.g.*, DHCR7, CYP2R1, GC genes) also affected outcomes (Moon [40], Motamed [35]).

DISCUSSION

Main findings

This integrative systematic review synthesises evidence from 64 randomised controlled trials (RCTs) evaluating vitamin D supplementation during pregnancy. A rigorous search strategy was employed using high-quality databases (PubMed and Cochrane Library), ensuring comprehensive inclusion of studies conducted across diverse populations and settings.

The overall findings indicate that vitamin D supplementation during pregnancy is safe and can be recommended as part of prenatal care, particularly in populations with widespread deficiency. While improvements in maternal and neonatal vitamin D status were consistently observed, its impact on specific clinical outcomes such as preeclampsia and gestational diabetes remains inconclusive. The most consistent benefit was seen with daily doses ≥ 2,000 IU, which appear to be most effective in correcting maternal deficiency and improving neonatal vitamin D levels.

Strengths and limitations

This review builds on extensive literature and includes a large number of RCTs published over the past decade. Its strength lies in the thematic organisation of findings, which provides practical guidance for clinicians and researchers despite the heterogeneity in trial design.

By grouping studies based on outcome domains (*e.g.*, maternal vitamin D status, metabolic effects, rare comorbidities), we were able to identify patterns in dosing efficacy and safety. This thematic synthesis enhances interpretability and supports decision-making in clinical practice.

However, significant variation across studies, in terms of dosing regimens, baseline vitamin D status, timing of supplementation, and outcome definitions, limited our ability to perform a meta-analysis. These differences underscore the need for more standardised reporting in future trials.

Additionally, many included studies lacked detailed data on adverse events or long-term child development, limiting conclusions regarding extended benefits or safety beyond pregnancy.

Interpretation and comparison with existing literature

Regarding the safe dose of vitamin D during pregnancy, global recommendations vary widely, from 200 to 4,000 IU/day. In line with recent evidence, our review confirms that supplementation up to 4,000 IU/day is generally safe, with no reported cases of hypercalcemia or toxicity across multiple trials Roth [45], Hollis [26], Nausheen [69]. Some authors have even suggested that higher daily doses up to 10,000 IU/day may be well tolerated in deficient populations, though further research is needed before such recommendations can be made broadly [1, 5].

The fat-soluble nature of vitamin D supports the potential use of intermittent dosing strategies, such as weekly or monthly boluses. Roth *et al*. [44-46] demonstrated the efficacy and safety of high-dose intermittent regimens in raising maternal and neonatal vitamin D concentrations. Such approaches may be particularly beneficial in low-resource settings where daily adherence is challenging. However, these regimens require further long-term evaluation to ensure comparable clinical benefits and avoid potential risks associated with fluctuating serum levels.

In addition to the commonly reported outcomes, emerging evidence suggests that adequate vitamin D status during pregnancy may reduce the risk of rare but clinically relevant complications, for example observational evidence links sufficient vitamin D levels with a lower risk of preterm birth and first-trimester abortion [74].

Case reports highlight associations between severe maternal vitamin D deficiency and unusual conditions such as neonatal craniotabes and pregnancy-associated transient osteoporosis of the hip [75, 76].

These findings emphasise the importance of identifying and addressing profound vitamin D deficiency, particularly in high-risk groups such as women with limited sun exposure, darker skin pigmentation, or poor dietary intake.

Despite compelling evidence of vitamin D's role in perinatal health, there remains a need for well-designed RCTs to establish optimal dosing strategies and clarify its impact on major pregnancy complications. Future trials should focus on populations with a high prevalence of vitamin D deficiency and incorporate subgroup analyses based on baseline status, genetic factors, and timing of supplementation.

Furthermore, while this review focuses on vitamin D supplementation, it is important to reinforce that dietary improvement and lifestyle modifications remain essential components of prenatal care. Supplementation becomes particularly critical during pregnancy when physiological demands increase and circulating vitamin levels often decline without intervention.

CONCLUSIONS

Despite inherent limitations that constrain definitive conclusions, several important findings emerged from this systematic review. Our analysis incorporates data from numerous trials not previously included in existing reviews, offering updated insights into the role of vitamin D supplementation during pregnancy. High-quality intervention stu-

dies support the beneficial effects of vitamin D on maternal, foetal, and early childhood health outcomes. Supplementation with 4,000 IU/day appears safe and most effective in improving maternal and neonatal 25(OH) D concentrations.
However, optimal dosing should consider individual factors such as baseline vitamin D status, ethnicity, gestational timing, and season of supplementation. These variables significantly influence the response to vitamin D supplementation and should guide clinical decision-making.
We hope these findings contribute to ongoing discussions and stimulate further research aimed at refining recommendations for vitamin D use in pregnancy, ultimately leading to improved maternal and child health outcomes.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution
B.H.A-I.: Conceptualization, data curation, formal analysis, writing – original draft. I.T.: Visualization, writing – review & editing.

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