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Efficacy of vitamin D supplementation on the incidence of preeclampsia: a systematic review and meta-analysis

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Abstract

Background Preeclampsia is a severe pregnancy complication affecting 2–8% of pregnancies globally, contributing to substantial maternal and fetal morbidity and mortality. Vitamin D deficiency has been associated with an increased risk of preeclampsia, yet the efficacy of its supplementation during pregnancy in reducing preeclampsia incidence remains uncertain.

Objectives This systematic review and meta-analysis aimed to evaluate the impact of vitamin D supplementation on the incidence of preeclampsia and related maternal and neonatal outcomes.

Method We systematically searched PubMed, Scopus, Cochrane Library, and Web of Science until August 2024 for randomized controlled trials (RCTs) examining the effects of vitamin D supplementation on preeclampsia. Eligible studies included pregnant women with varying doses of vitamin D supplementation compared to placebo or standard care. Primary outcomes were the incidence of pre-eclampsia and preterm labor; secondary outcomes included serum 25-hydroxyvitamin D levels, low birth weight, and APGAR scores. Data were synthesized using R statistical software, with effect measures reported as relative risk (RR) and mean difference (MD) with a 95% confidence interval (CI).

Results A total of 33 RCTs involving 10,613 participants were included. Vitamin D supplementation significantly reduced the risk of preeclampsia by 44.8% (RR = 0.55, 95% CI [0.43, 0.71], $P < 0.0001$) and preterm labor by 30% (RR = 0.70, 95% CI [0.51, 0.96], $P = 0.0286$). Subgroup analyses indicated that the benefits were more pronounced when the control group received a placebo rather than low-dose vitamin D. Serum 25-hydroxyvitamin D levels significantly increased in the supplementation group (MD = 32.42 nmol/L, 95% CI [20.33, 44.50], $P < 0.0001$). However, no significant differences were observed in the incidence of low birth weight (RR = 0.65, 95% CI [0.42, 1.02], $P = 0.057$) or Apgar scores at 5 min (MD = 0.20, 95% CI [-0.01, 0.40], $P = 0.057$).

Conclusion Vitamin D supplementation during pregnancy significantly reduces the risk of preeclampsia and preterm labor, though its impact on neonatal outcomes remains unclear. These findings underscore the potential value of

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vitamin D supplementation in prenatal care for improving maternal outcomes. Further research is needed to clarify its effects on neonatal health.

Keywords Vitamin D, Preeclampsia, Pregnancy, Preterm labor, Systematic review, Meta-analysis

Introduction

Globally, preeclampsia accounts for 2–8% of all pregnancy-related problems, killing over 50,000 mothers and over 500,000 fetuses [1]. It occurs when a woman whose blood pressure was normal before pregnancy develops abnormally high blood pressure during or after the 20th week of gestation. Blood pressure of 140/90 mmHg or above, edema, and proteinuria with multiorgan failure are further symptoms of preeclampsia. A significant cause of preterm delivery (i.e., pregnancy delivered before 37 weeks of gestation), the condition can have catastrophic consequences. Severe cases that impact brain function, leading to seizures or coma, are called eclampsia [2–4]. HELLP syndrome is a life-threatening form of preeclampsia characterized by hemolysis, elevated liver enzymes, and low platelets and may occur without hypertension or proteinuria. Preeclampsia can be divided into two subtypes: early-onset (or placental) and late-onset (or maternal) preeclampsia [5]. Early-onset preeclampsia is due to a defective placenta [6] and maternal preeclampsia is due to maternal endothelial dysfunction [7]. The term "postpartum preeclampsia" is used to describe a form of preeclampsia that often appears within 48 h to six weeks following the delivery [8]. Postpartum preeclampsia can occur regardless of the occurrence of high blood pressure or preeclampsia during pregnancy [9]. Pre-eclampsia in a subsequent pregnancy is eight times higher in patients with a history of preeclampsia [10]. Several serious complications can occur in preeclamptic patients, including hypertension, eclampsia, pulmonary edema, myocardial infarction, stroke, acute respiratory distress syndrome (ARDS), renal and retinal injury, and fetal complications such as growth restrictions, placental abruption, or maternal or fetal death [2, 11]. Some studies suggest an association between vitamin D deficiency and preeclampsia [12, 13, 14]. Vitamin D deficiency is common among high-risk pregnant women [15]. Vitamin D decreases pro-inflammatory response [16] and upregulates genes associated with placental invasion and normal implantation [16], which can affect inflammation and abnormal placental invasion. Vitamin D can affect vascular endothelial dysfunction by improving vascular structure, elasticity, and intima-media thickness, decreasing blood pressure [17], and reducing oxidative stress [18]. It can also alter the proteinuria caused by renal vascular endothelial growth factors (VEGF) as it increases vascular smooth muscle cell proliferation by increasing VEGF gene transcription [19]. Despite all the effects of vitamin D, there is no clear evidence of whether to use it for pregnancy. Since the problem of preeclampsia is significant and there is no clear consensus on the usage of vitamin D in pregnancy, we conducted this systematic review and meta-analysis of all relevant randomized controlled trials (RCTs) to determine the effects of vitamin D supplementation during pregnancy on the incidence of preeclampsia.

Methodology

We conducted the study following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [20]. The study protocol was prospectively registered on the International Prospective Register of Systematic Reviews PROSPERO (CRD42024580640).

Information sources and search strategy

We searched the databases PubMed, Scopus, Cochrane Library, and Web of Science to identify the relevant studies up to August 2024. The search strategy was (vitamin D) AND (preeclampsia OR "Pre-Eclampsia"[Mesh] OR toxemia OR gestosis OR gestational hypertension OR eclampsia OR (birth weight) OR "Infant, Low Birth Weight"[Mesh] OR "Birth Weight"[Mesh] OR (preterm birth) OR "Premature Birth"[Mesh]). Following the database search, duplicates were removed, and titles and abstracts were screened using Rayyan software [21]. Initially, we had 11,204 studies in total, and after duplicate removal, we had 8765 studies. We performed title and abstract screening, yielding 57 studies. Then, full-text screening was performed, yielding 33 studies (Fig. 1).

Eligibility criteria

Participants

We included only RCTs; other study designs were excluded. this inclusion criterion was pregnant women taking vitamin D supplementation to explore its preventive effects against preeclampsia and related complications. The comparator group consisted of pregnant women taking a placebo, standard care, or low doses of vitamin D ≤ (400 IU/day). The outcomes of interest and primary were preeclampsia, preterm labor, and measurement of 25-hydroxyvitamin D. Secondary outcomes included baby outcomes such as low Apgar score at 5 min and low birth weight.

Standard care

Standard care for pregnant women refers to routine practices that support maternal and fetal health during

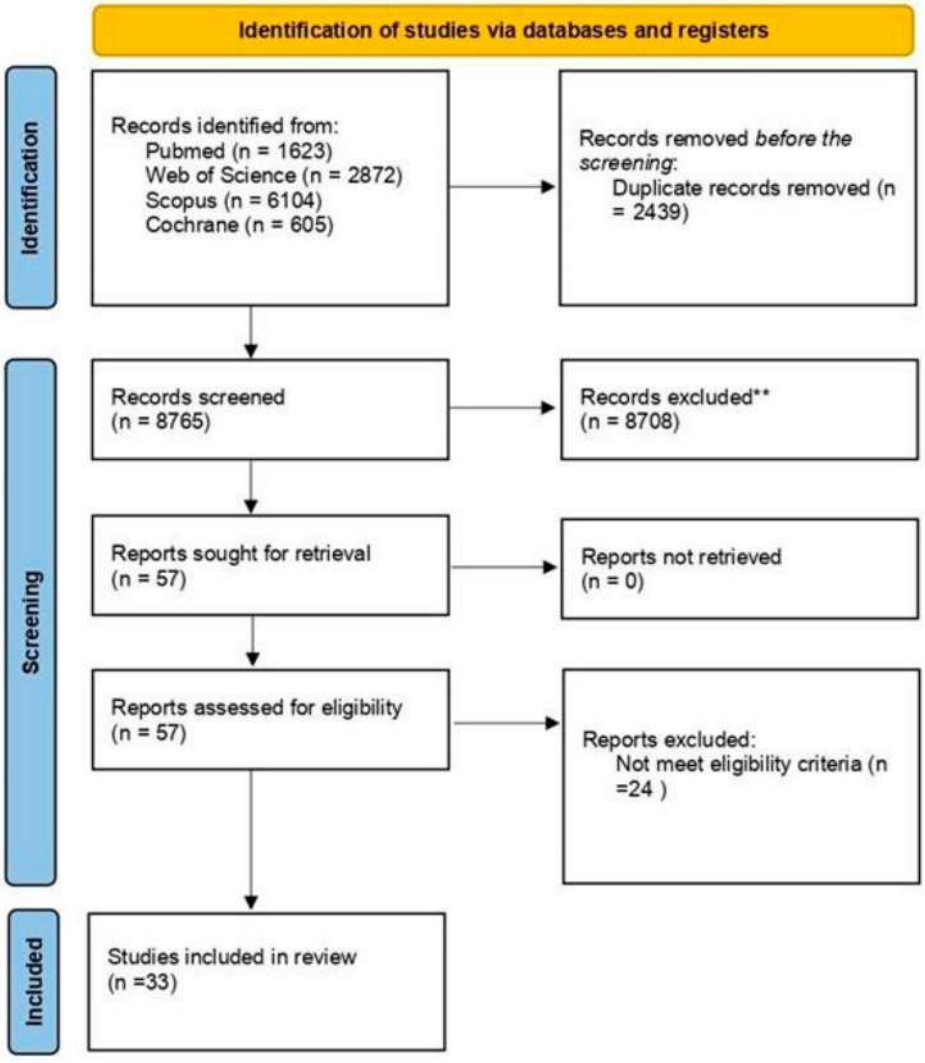

Fig. 1 Prisma flow diagram

pregnancy. It normally includes regular contact with antenatal care providers to monitor and perform maternal and fetal assessments, give nutritional advice and needed supplementations, and conduct preventive interventions and counseling. For example, pregnant women are often provided with daily iron (30–60 mg) and folic acid (400 μg) supplementation to prevent anemia and low birth weight.

Study selection and data extraction

Two independent authors blinded to each other extracted the data of each study using a uniform Google sheet; disagreements were resolved by consensus or referring to the primary investigator. Data extracted involved the participant's baseline characteristics (number, age, baseline 25-hydroxy vitamin D, gestational age, DBP, SBP, BMI, height, weight, parity), included studies' characteristics (study ID, location, year, study design, population, intervention, comparator, start point of intervention, duration of intervention, outcomes), and outcome measures (preeclampsia, preterm labor, measurement of 25-hydroxyvitamin D).

Risk of bias and quality assessment

Two independent blinded authors assessed the quality of the included RCTs using the Cochrane risk-of-bias tool 2 (RoB-2) [22], which contains six domains: (1) randomization process (2), deviation from the intended interventions (3), missing outcome data (4), measuring outcome (5), selection of the reported outcome, and (6) other bias. The investigators' conclusions are classified as "low risk," "no information,"" some concerns," or "high risk" of bias for each of these topics. A third investigator reanalyzed the disagreements and resolved them. The RoB-2 tool

summary and graph were produced using the Robvis [22].

Effect measures and data synthesis

The primary outcomes were pre-eclampsia, preterm labor, and measurement of 25-hydroxyvitamin D. In data analysis, categorical variables were represented as counts and percentages, and continuous variables were reported as mean and standard deviation (SD). If needed, the median and interquartile range (IQR) were converted to mean and SD using the formula provided by Wan et al. [23]. We employed the Web Plot Digitizer program to extract data from graphs. All meta-analyses were performed using R Statistical Software (v4.4.1; R Core Team 2024). Continuous data were pooled as mean difference (MD) or standardized mean difference (SMD) with a 95% confidence interval (CI). In contrast, dichotomous data were pooled as risk ratio (RR) with a 95% CI.

Heterogeneity assessment and sensitivity analysis

A visual inspection of the final forest plots and an assessment by I-square (I^2) and Chi-Square tests (X^2) were conducted to identify the degree of heterogeneity. In case of significant heterogeneity ($X^2P<0.1$), the random effect model has been used to resolve heterogeneity using R programming code.

Subgroup analysis

Based on the difference between control group supplementation, we performed a subgroup analysis.

Results

Search and screening

This search retrieved 11,204 potentially relevant publications; 2439 duplicates were removed, and 8765 remained for a title and abstract screening. After the abstract screening, 57 papers were eligible for full-text screening. Out of them, 33 RCTs with 10,613 patients were included. 24 publications were excluded: outcomes measured in one RCT did not meet the inclusion criteria, and publications did not meet abstracts or protocols of already included studies. These details are provided in Fig. 1.

Characteristics of the included studies

All studies were RCTs where pregnant patients were allocated to receive either the vitamin D supplement or the placebo intervention. All thirty-three studies provided vitamin D at a variable daily dose ranging from 400 IU/day to 200,000 IU (single dose). Standard Care: Several interventions included standard care, such as iron, calcium, and folic acid supplementation provided alongside vitamin D in various groups. Routine antenatal care in groups that received vitamin D and other vitamin/mineral supplements (Table 1).

Risk of bias assessment

Among the included studies, eleven [24–34] were rated as having a low risk of bias across all domains, indicating a robust methodological approach. However, nine studies [35–43] were identified with a high risk of bias, increasing risks of the potential impact of bias on their findings. Moreover, thirteen studies [44–56] identified concerns that received an unclear rating in at least one domain, indicating the need for further clarification in study reporting. Besides, the summary plot for domains shows that the first domain," Bias arising from the randomization process," has the most studies with some concerns. **(**Fig. 2**)**

Outcomes

Maternal data

The meta-analysis of 15 studies involving 5,035 participants revealed that Vitamin D supplementation significantly reduces the risk of preeclampsia. The random-effects model showed a risk ratio (RR) of 0.5519 (95% CI: 0.4296–0.7090, $p<0.0001$), indicating a 44.8% reduction in risk compared to the control group. Heterogeneity was low to moderate, with $I^2 = 34.4\%$, and the Q-test for heterogeneity was not statistically significant ($p=0.0929$). Subgroup analysis based on the type of control group showed that the reduction in preeclampsia risk was more pronounced when the control group received a placebo (Vitamin D-free) (RR=0.5150, 95% CI: 0.4079–0.6502, $I^2 = 19.4\%$) compared to a low dose of Vitamin D (RR=0.7308, 95% CI: 0.3718–1.4367, $I^2 = 34.4\%$). However, the test for subgroup differences ($p=0.3372$) indicated no statistically significant variation between these groups. These findings highlight the potential benefit of vitamin D supplementation in reducing preeclampsia risk, particularly in populations with minimal baseline vitamin D intake (Fig. 3). The analysis also included 13 studies with 6055 participants (3429 in the experimental group and 2626 in the control group) and 541 events. Vitamin D supplementation significantly reduced the risk of preterm labor, with an overall RR of 0.6999 (95% CI: 0.5085–0.9633, $p=0.0286$), indicating a 30% lower risk compared to the control group. Heterogeneity among studies was moderate ($I^2 = 59.7\%$, $p=0.0030$). Subgroup analysis revealed that the reduction in preterm labor risk was more pronounced when the control group received a placebo (RR=0.5838, 95% CI: 0.4100–0.8312, $I^2 = 55.1\%$) than when it received low-dose vitamin D (RR=1.1977, 95% CI: 0.8010–1.7908, $I^2 = 0\%$). The test for subgroup differences was statistically significant ($p=0.0085$), suggesting that vitamin D supplementation was more effective in reducing preterm labor risk when

Table 1 Study characteristics and demographics of the population

Study ID	Location	Year	Study Design	Population (Inclusion Criteria)	Intervention (Dose, Route, Name)	Comparator	Start-Point of Intervention (Weeks)	Duration of Intervention (Weeks)	Outcomes (Primary and Secondary)	Key Findings
Ali et al. 2019 [36]	Saudi Arabia	2018	Randomized Controlled Trial	Maternal age 20–40 years; singleton pregnancy < 13 weeks	G1: 400 IU vitamin D3 daily; G2: 4000 IU vitamin D3 (40 drops daily)	Low dose 400 IU/day	6–12	Till 3 months postpartum	Primary: Preeclampsia; Secondary: Change in vitamin D levels at 36th week of pregnancy	Vitamin D3 reduced pre-eclampsia risk; 4000 IU improved serum levels; lower IUGR incidence.
Asemi et al. 2015 [44]	Iran	2015	Randomized Controlled Trial	Pregnant women at risk of preeclampsia; primigravida aged 18–40 years with singleton pregnancy in the third trimester	800 mg calcium, 200 mg magnesium, 8 mg zinc, 400 IU vitamin D3	Placebo	25	9	Preeclampsia, vitamin D levels, cesarean section rate, gestational age, newborn weight, length, gestational diabetes rate	Multi-mineral vitamin D increased newborn length; no impact on gestational age; BP decreased.
Azami et al. 2017 [35]	Iran	2014	Randomized Controlled Trial	Women > 20 weeks of gestational age with at least one preeclampsia risk factor	G1: Ferrous sulfate + 800 mg Ca, 200 mg Mg, 8 mg Zn, 400 IU vitamin D3 daily; G2: Ferrous sulfate + vitamin C (250 mg) and E (55 mg)	Control (ferrous sulfate only)	20	Till delivery	Preeclampsia, neonatal complications	Group A had lower pre-eclampsia; vitamins C/E ineffective for prevention; cost-effective for high-risk.
Ashraf et al. 2023 [45]	Iran	2023	Randomized Controlled Trial	250 pregnant women	50,000 IU vitamin D3 capsule every 2 weeks	Control	> 20	Till 36 weeks of gestation	Development of pre-eclampsia, pregnancy outcomes (mode of delivery, spontaneous vaginal delivery, abortion), blood pressure, proteinuria	Vaginal deliveries: 62.4% (intervention), 49.6% (control); no significant delivery type differences.
Brooke et al. 1980 [46]	UK	2016	Randomized Controlled Trial	59 women received supplementation, 67 controls	Ergocalciferol (1000 IU/day)	Placebo	28–32	Last trimester	Maternal and infant vitamin D, calcium levels, hypocalcemia in infants, infant size and growth outcomes	Higher plasma calcium in treatment group; seasonal variation in plasma 25-OHD levels observed.
Cooper et al. 2016 [47]	UK	2016	Randomized Controlled Trial	965 pregnant women	Cholecalciferol 1000 IU/day orally	Placebo	14	Till delivery	Neonatal whole-body bone mineral content assessed by DXA within 2 weeks of birth	No neonatal BMC difference; higher maternal 25(OH)D; severe PPH lower in cholecalciferol group.
Delvin et al. 1986 [48]	France	1986	Randomized Controlled Trial	40 pregnant women	1000 IU vitamin D3/day	Control	27	Till delivery	Maternal 25-hydroxyvitamin D (ng/mL) and 1,25-dihydroxyvitamin D (pg/mL)	Maternal/neonatal 25-OHD levels improved; maternal stores crucial for neonatal calcium handling.

Table 1 (continued)

Study ID	Location	Year	Study Design	Population (Inclusion Criteria)	Intervention (Dose, Route, Name)	Comparator	Start-Point of Intervention (Weeks)	Duration of Intervention (Weeks)	Outcomes (Primary and Secondary)	Key Findings
Grant et al. 2014 [24]	New Zealand	2014	Randomized Controlled Trial	Pregnant women 26–30 weeks gestation; singleton pregnancy	Pregnant women: 1000 IU or 2000 IU vitamin D3 daily; Infants: 400 IU or 800 IU vitamin D3	Placebo	27	9	Serum 25(OH)D ≥ 30 ng/mL in infants; hypercalcemia incidence	Higher serum levels in high-dose group; no hypercalcemia in infants; vitamin D compliance similar.
Hossain et al. 2014 [37]	Pakistan	2014	Open-label, Randomized Trial	207 pregnant women ≤ 20 weeks gestation; singleton pregnancy; normoglycemic and normotensive	Oral 4000 IU vitamin D3 daily; routine antenatal care in both arms	Routine care (iron and calcium supplementation)	20	Till delivery	Incidence of pre-eclampsia, gestational hypertension, cesarean section rate, birth weight, Apgar score	Vitamin D raised maternal/neonatal 25OHD; most neonatal parameters unaffected; persistent deficiency.
Kabuyanga et al. 2024 [49]	Congo	2024	Single-blind, Randomized Trial	Primigravidae; singleton pregnancy ≤ 16 weeks gestation	60,000 IU vitamin D orally monthly	Control	16	Till delivery	Primary: Preeclampsia incidence; Secondary: Preterm delivery, birth weight and height, mode of delivery, APGAR score	Reduced preeclampsia, preterm delivery; better neonatal outcomes in supplemented group.
Karamali et al. 2015 [25]	Iran	2015	Randomized Controlled Trial	Pregnant women (primigravida), aged 18–40 years, at risk for pre-eclampsia	Oral pearl containing 50,000 IU vitamin D3 every 14 days	Placebo	20 weeks of gestation	12 weeks	Pre-eclampsia rate, low birth weight (LBW) (< 2500 g), newborn's birth size, preterm delivery (< 37 weeks), metabolic concentrations, inflammatory biomarkers, oxidative stress, and blood pressures	Cholecalciferol improved insulin levels, HOMA-IR, and HDL; no effect on fasting glucose or outcomes.
Kaur et al. 1991 [39]	India	1991	Randomized Controlled Trial	Pregnant women without complications (e.g., pre-eclampsia, antepartum hemorrhage, premature delivery, twins, or systemic diseases)	Two pharmacological doses of 60,000 IU vitamin D3 in the 6th and 7th month of pregnancy	No supplementation	25 weeks of gestation	4 weeks	Birth weight, placental weight, placental protein, DNA, RNA contents	Increased birth/placental weights in the supplemented group; protein/DNA/RNA contents higher.
Khan et al. 2016 [50]	Pakistan	2016	Randomized Controlled Trial	Pregnant females at 12–16 weeks of gestation	An oral dose of 4000 IU vitamin D daily	Placebo	12–16 weeks of gestation	~26 weeks	Birth weight (kg), vitamin D levels (ng/mL)	LBW incidence: 29%; no birth weight difference; periodontal improvement; insufficient vitamin D.

Table 1 (continued)

Study ID	Location	Year	Study Design	Population (Inclusion Criteria)	Intervention (Dose, Route, Name)	Comparator	Start-Point of Intervention (Weeks)	Duration of Intervention (Weeks)	Outcomes (Primary and Secondary)	Key Findings
Ku et al. 2024 [38]	Singapore	2024	Non-blinded Randomized Controlled Trial	274 pregnant women	800 IU/day	400 IU/day	16 weeks of gestation	24–28 weeks of gestation	Maternal serum 25OHD and lipid levels, fasting glucose, 1 h/2 h post-load glucose, gestational diabetes, gestational hypertension, pre-eclampsia, cesarean section, gestational weight gain, birth outcomes (e.g., weight, length, head circumference, preterm birth, low birth weight, neonatal special care)	77.7% achieved sufficient 25OHD; lower LBW; no significant maternal/birth outcomes differences.
Mallet et al. 1986 [40]	France	1986	Randomized Controlled Trial	77 white pregnant women aged 18–36 years in the last trimester of pregnancy living in Northwest France	Group 1: Daily oral 1000 IU vitamin D (ergocalciferol-D2) for the last 3 months; Group 2: Single oral dose of 200,000 IU vitamin D at 7 months	Group 3: Control group	Group 1: Week 29–40; Group 2: Week 29	12 weeks	Maternal: 25OHD, 1,25(OH)2D (nmol/L); Infant: birth weight (grams)	NR
Memon et al. 2022 [51]	Pakistan	2022	Randomized Controlled Trial	90 pregnant women aged 18–35 years with single pregnancies, normal BP, and gestational period of 24 ± 1 week	Vitamin D 25,000 IU orally (cholecalciferol) every 2 weeks; iron, calcium, and folic acid supplementation added in both groups	Routine care (iron and calcium supplementation)	23–25 weeks	36 weeks	Incidence of pre-eclampsia	Reduced preeclampsia risk (6.66% vs. 24.44% in control); proteinuria higher in controls.
Mohammad-Alizadeh-Charandabi et al. 2015 [26]	Iran	2015	Randomized Controlled Trial	124 pregnant women aged 18–39 years with gestational age 25–30 weeks	Group 1: Daily 300 mg carbonate calcium + 1000 IU vitamin D; Group 2: Daily 1000 IU vitamin D supplements for 8.5 weeks	Placebo	NA	Till delivery	Birth weight (kg), birth height (cm), head circumference at birth (cm), duration of pregnancy (days), mode of delivery	No significant neonatal or pregnancy outcome differences; future larger studies are needed.

Table 1 (continued)

Study ID	Location	Year	Study Design	Population (Inclusion Criteria)	Intervention (Dose, Route, Name)	Comparator	Start-Point of Intervention (Weeks)	Duration of Intervention (Weeks)	Outcomes (Primary and Secondary)	Key Findings
Moon et al. 2022 [53]	UK	2022	Randomized Controlled Trial	Pregnant women > 18 years old, singleton pregnancy, gestational age < 17 weeks (based on LMP/ultrasound)	Cholecalciferol 1000 IU/day + standard antenatal care (400 IU/day)	Placebo + standard antenatal care (400 IU/day)	14 weeks of gestation	Till delivery	25OHD concentration, gestational age at birth, mode of delivery, postpartum hemorrhage (> 500 mL)	Cholecalciferol increased vaginal deliveries and lowered instrumental/post-partum hemorrhage rates.
Mirzakhani et al. 2016 [52]	USA	2011	Randomized Controlled Trial	Pregnant women aged 18–40 years, at high risk of atopic disease, 10–18 weeks pregnant, non-smokers	4000 IU vitamin D daily + multivitamin with 400 IU vitamin D (total: 4400 IU/day)	400 IU vitamin D	10–18 weeks of gestation	Till delivery	Preeclampsia, 25(OH)D concentration	Sufficient vitamin D reduced preeclampsia risk; no reduction in incidence with supplementation.
Naghshineh et al. 2016 [27]	Iran	2016	Randomized Controlled Trial	Pregnant women < 16 weeks gestation, no vitamin D deficiency, no aspirin use, and no diagnosis of chronic hypertension, gestational diabetes, renal disease, or systemic lupus erythematosus	600 IU daily vitamin D	Placebo	< 16 weeks gestation	Till delivery	Outcomes not specified	Preeclampsia/preterm labor is lower in the supplemented group; higher birth weight.
Rodda et al. 2015 [28]	Australia	2015	Open-label randomized controlled trial	78 women with singleton pregnancies and vitamin D deficiency/insufficiency (serum 25-OH Vit D < 75 nmol/L) at their first antenatal appointment at 12–16 weeks gestation	Vitamin D (2000–4000 IU cholecalciferol) orally daily until delivery	Placebo	12–16	~12 (till delivery)	Neonatal and maternal serum 25-OH vitamin D concentration at delivery (nmol/L)	Increased neonatal/maternal 25-OH vitamin D; no adverse effects; routine screening recommended.
Rostami et al. 2018 [41]	Iran	2018	Randomized controlled trial	Pregnant women (18–40 years old) with gestational age < 14 weeks, singleton pregnancy, not consuming multivitamins with > 400 IU/day of D3, no chronic diseases	Based on the severity of Vit. D deficiency	Control	9–12	Not clearly mentioned	Preterm delivery, preeclampsia, GDM, 24-hour proteinuria	Screening improved 25(OH)D, and reduced preeclampsia (60%), GDM (50%), and preterm delivery (40%).
Roth et al. 2013 [29]	Bangladesh	2013	Randomized controlled trial	160 pregnant women aged 18–<35 years; gestational age 26–<30 weeks; planned to deliver at Shimantik maternity center and remain in Dhaka throughout pregnancy and postpartum	Weekly oral vitamin D3 (35,000 IU, Vigantol Oil) and prenatal iron/folic acid supplementation	Placebo with iron/folic acid supplementation	26–29	~12 (till delivery)	Maternal: serum 25-hydroxyvitamin D concentration (nmol); Infant: growth, postnatal vitamin D status (nmol)	High-dose vitamin D increased maternal/neonatal 25(OH)D; no hypercalcemia; transient hypercalciuria.

Table 1 (continued)

Study ID	Location	Year	Study Design	Population (Inclusion Criteria)	Intervention (Dose, Route, Name)	Comparator	Start-Point of Intervention (Weeks)	Duration of Intervention (Weeks)	Outcomes (Primary and Secondary)	Key Findings
Roth et al. 2018 [30]	Bangladesh	2018	Randomized, double-blind, placebo-controlled trial	1300 generally healthy pregnant women, gestational age 17–24 weeks	Three groups received prenatal oral vitamin D3 (4200 IU, 16,800 IU, 28,000 IU daily)	Placebo	17–24	~12 (till delivery)	Maternal: serum 25-hydroxyvitamin D levels (nmol); Infant: length-for-age, birth outcomes, morbidity, serum 25-hydroxyvitamin D levels (nmol)	Supplementation did not affect infant growth; increased maternal levels; no significant AEs.
Sabet et al. 2012 [54]	Iran	2012	Randomized controlled trial	50 pregnant women in their third trimester scheduled for delivery at Mahdieh Hospital	Vitamin D3 (100,000 IU/month orally, 3 times)	Placebo	27+ (third trimester)	~12 (till delivery)	Maternal: serum 25(OH)D concentration at delivery (nmol); Infant: serum vitamin D levels (ng/mL)	- Maternal 25(OH) VitD: 61.45 ng/mL vs. 29.4 ng/mL. - Cord blood 25(OH) VitD: 52 ng/mL vs. 36 ng/mL. - Higher prevalence of deficiency in control group newborns. - No significant difference in maternal serum iPTH levels. - Monthly 100,000 IU is safe for pregnant women.
Sablok et al. 2015 [42]	India	2015	Randomized controlled trial	180 primigravidae with singleton pregnancies at 14–20 weeks gestation	Vitamin D (dosage based on initial levels: a single dose of 60,000 IU for sufficient levels; two doses of 120,000 IU for insufficient; four doses of 120,000 IU for deficient levels)	Control	14–20	~20 (till delivery)	Gestational hypertension, preeclampsia, GDM, birth weight (kg)	- Maternal 25(OH) VitD levels improved. - Higher preterm labor rates and lower birthweight in Group A. - High-dose reduced gestational hypertension and pre-eclampsia.
Samimi et al. 2017 [31]	Iran	2017	Randomized controlled trial	80 pregnant women with recurrent miscarriage (≥ 2 consecutive or ≥ 3 non-consecutive)	Vitamin D3 (400 IU/day orally) + vaginal progesterone (400 mg/day to both groups)	Placebo	Not applicable	~20 (till delivery)	Spontaneous abortion rate, vitamin D levels (ng/mL)	- Vitamin D3 reduced IL-23 levels and increased serum levels. - Abortion rate: Control 34.2% vs. Intervention 12.8%. - IL-23 correlated with abortion. - Suggested effect via IL-23 pathway.

Table 1 (continued)

Study ID	Location	Year	Study Design	Population (Inclusion Criteria)	Intervention (Dose, Route, Name)	Comparator	Start-Point of Intervention (Weeks)	Duration of Intervention (Weeks)	Outcomes (Primary and Secondary)	Key Findings
Sasan et al. 2017 [32]	Iran	2017	Randomized controlled trial	142 pregnant women (25-hydroxyvitamin D ≥ 25 ng/mL) receiving prenatal care with, history of preeclampsia	Vitamin D3 (50,000 IU every two weeks)	Placebo	Not clearly mentioned	~20 (till delivery)	Maternal: preeclampsia incidence, mode of delivery	- Reduced preeclampsia recurrence risk. - The control group had a 1.94x higher risk. - – 15.7% in the intervention group experienced preeclampsia.
Shahgheibi et al. 2016 [33]	Iran	2016	Randomized controlled trial	90 pregnant women with at least one risk factor for GDM (BMI > 25, macrosomic history, family history of diabetes, gestational diabetes in prior pregnancy, or glycosuria)	Vitamin D (5000 IU/week)	Placebo	Not clearly mentioned (~first two trimesters)	~14 (till 26 weeks)	Maternal: systolic and diastolic BP, type of delivery; Infant: birth weight, Apgar score	- Reduced gestational diabetes incidence in high-risk women. - No significant differences in blood pressure or birth weight.
Singh et al. 2015 [43]	India	2014	Randomized controlled trial	100 healthy primigravidae, singleton pregnancies, gestational age 12–16 weeks	Vitamin D3 (2000 IU/day orally)	No supplementation	12–16	~20 (till delivery)	Maternal: vitamin D levels, mode of delivery (preterm, full term, cesarean); Infant: birth weight, Apgar score	- Reduced preterm birth rates and increased birth weight. - No maternal/neonatal mortality. - Higher cesarean rates linked to deficiency.
Sunarno et al. 2023 [55]	Indonesia	2023	Randomized controlled trial	108 pregnant mothers at 20 weeks with systolic BP 110–140 mmHg, diastolic BP 70–90 mmHg, and serum calcidiol < 30 ng/mL	Group 1: 15-min sunbathing daily; Group 2: Vitamin D3 1000 IU/day for 17 weeks	Placebo	20 weeks	17 weeks	Maternal: calcidiol levels, systolic and diastolic BP; Fetal: birth weight, birth length, head circumference	- Increased Calcidiol levels. - Sun exposure increased Calcidiol and birth weight. - Vitamin D increased birth weight by 302.26 g.

Table 1 (continued)

Study ID	Location	Year	Study Design	Population (Inclusion Criteria)	Intervention (Dose, Route, Name)	Comparator	Start-Point of Intervention (Weeks)	Duration of Intervention (Weeks)	Outcomes (Primary and Secondary)	Key Findings
Vaziri et al. 2016 [34]	Iran	2016	Randomized controlled trial	127 pregnant women (≥ 18 years), no history of mental illness, no substance abuse, single viable fetus at 26–28 weeks	Group 1: 2000 IU Vitamin D3 daily	Placebo	26–28 weeks	Till delivery	Maternal: baseline and childbirth 25(OH)D concentrations; Infant: 25(OH)D concentrations, anthropometric measures at birth, 4th, and 8th weeks of life	- No significant difference in vitamin D status over time. - No difference in infant/maternal bone mass. - Taller infants for multiparous mothers.
Yu et al. 2009 [56]	UK	2009	Randomized controlled trial	180 pregnant women (45 Indian Asians, 45 Middle Eastern, 45 Black, 45 Caucasian) at 27 weeks with no major illnesses	Group 1: Vitamin D2 800 IU daily; Group 2: Single oral dose of 200,000 IU calciferol; Group 3: no treatment	Placebo	27 weeks	Till delivery	Maternal: maternal and cord 25(OH)D levels at delivery; Infant: small-for-gestational-age (< 10th percentile for adjusted gestation, sex, maternal ethnicity, parity, height, and weight)	- Higher maternal and cord vitamin D levels with supplementation. - Lower secondary hyperparathyroidism in supplemented women.

IU, international unit; G1, Group 1; G2, Group 2; ca, calcium; mg, magnesium; Zn, zinc; BP, blood pressure; DXA, dual-energy X-ray absorptiometry; BMC, bone mineral content; IUGR, intrauterine growth restriction; PPH, postpartum hemorrhage; 25-OHD, 25-hydroxyvitamin D; HOMA-IR, homeostatic model assessment for insulin resistance; HDL, high-density lipoprotein; LBW, low birth weight; GDM, gestational diabetes mellitus; iPTH, intact parathyroid hormone; IL, interleukin

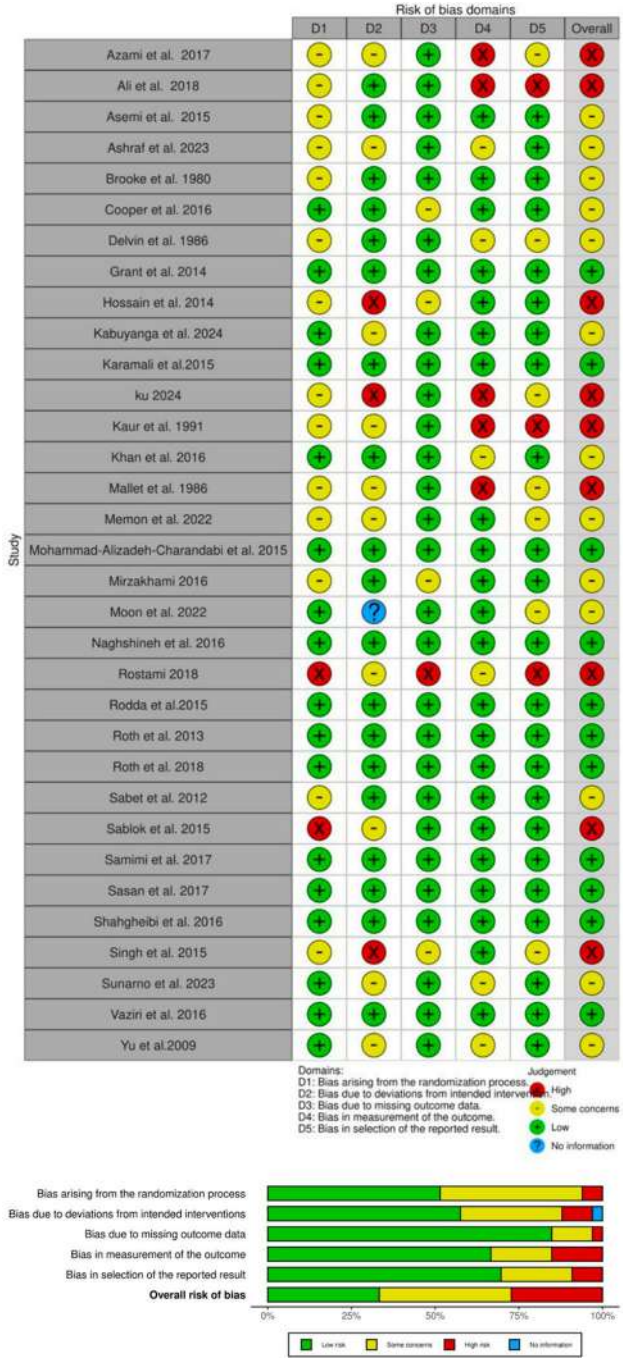

Fig. 2 'Risk of bias graph': review authors' judgments about each risk of bias item presented as percentages across all included studies, and 'Risk of bias summary': review authors' judgments about each risk of bias item for each included study

compared to placebo rather than low-dose supplementation. These findings highlight the potential of vitamin D as an intervention to lower the risk of preterm labor, especially in populations without baseline supplementation (Fig. 4). This indicates that vitamin D supplementation is associated with a 30% lower risk of preterm labor than controls. Additionally, the measurement of serum 25-hydroxyvitamin D levels revealed an MD of 32.42 nmol/L (95% CI: [20.33, 44.50], $P<0.0001$) (Fig. 5), highlighting a significant increase in vitamin D levels among those who received supplementation.

Infant Data

In contrast, data from 7 studies assessing the incidence of low birth weight did not demonstrate a statistically significant difference between the two groups, with a pooled risk ratio of 0.65 (95% CI: [0.42, 1.02], $P=0.0568$). Heterogeneity among studies was moderate (I^2 = 65%, $p<0.01$) (Fig. 6). This suggests that while there is a trend towards lower incidence rates of low birth weight in the vitamin D group, the results do not reach statistical significance. Similarly, the analysis of Apgar scores at 5 min post-delivery showed a mean difference of 0.2 (95% CI: [-0.01, 0.40], $P=0.0571$). Heterogeneity among studies was mild ($I^2 = 73\%$, $p=0.01$) (Fig. 7), indicating no significant difference in neonatal outcomes between the vitamin D supplementation group and controls.

Interpretation.

These findings suggest that vitamin D supplementation during pregnancy may significantly reduce the risks of preeclampsia and preterm labor in mothers. However, the lack of significant differences in low birth weight and Apgar scores indicates that while maternal outcomes improve with supplementation, the benefits may not extend to specific infant outcomes. Further research is warranted to explore these associations and clarify the potential impact of vitamin D on neonatal health.

Start time and duration

The body of research on vitamin D supplementation during pregnancy reveals nuanced findings regarding maternal and infant health. Roth et al. (2018) [30] studied 1,300 generally healthy pregnant women between 17 and 24 weeks of gestation until delivery, reporting no significant impact of supplementation on infant growth. In contrast, Sabet et al. (2012) [54] observed 50 third-trimester pregnant women in Tehran and found that those receiving 100,000 IU of monthly vitamin D supplementation had elevated 25(OH) vitamin D levels in both serum and cord blood, while the control group displayed a higher incidence of vitamin D deficiency. Although maternal serum iPTH levels showed no significant differences, the study emphasized the safety of supplementation, warranting further investigation into long-term effects. Supporting this, Khan et al. (2016) [52] monitored pregnant women from 12 to 16 weeks gestation for low birth weight (LBW) and reported an incidence of 29%, yet noted no overall differences in birth weight. Sunarno et al. (2023) [55], focusing on 108 pregnant mothers with specific blood pressure and low serum calcidiol levels, found that supplementation not only increased calcidiol levels

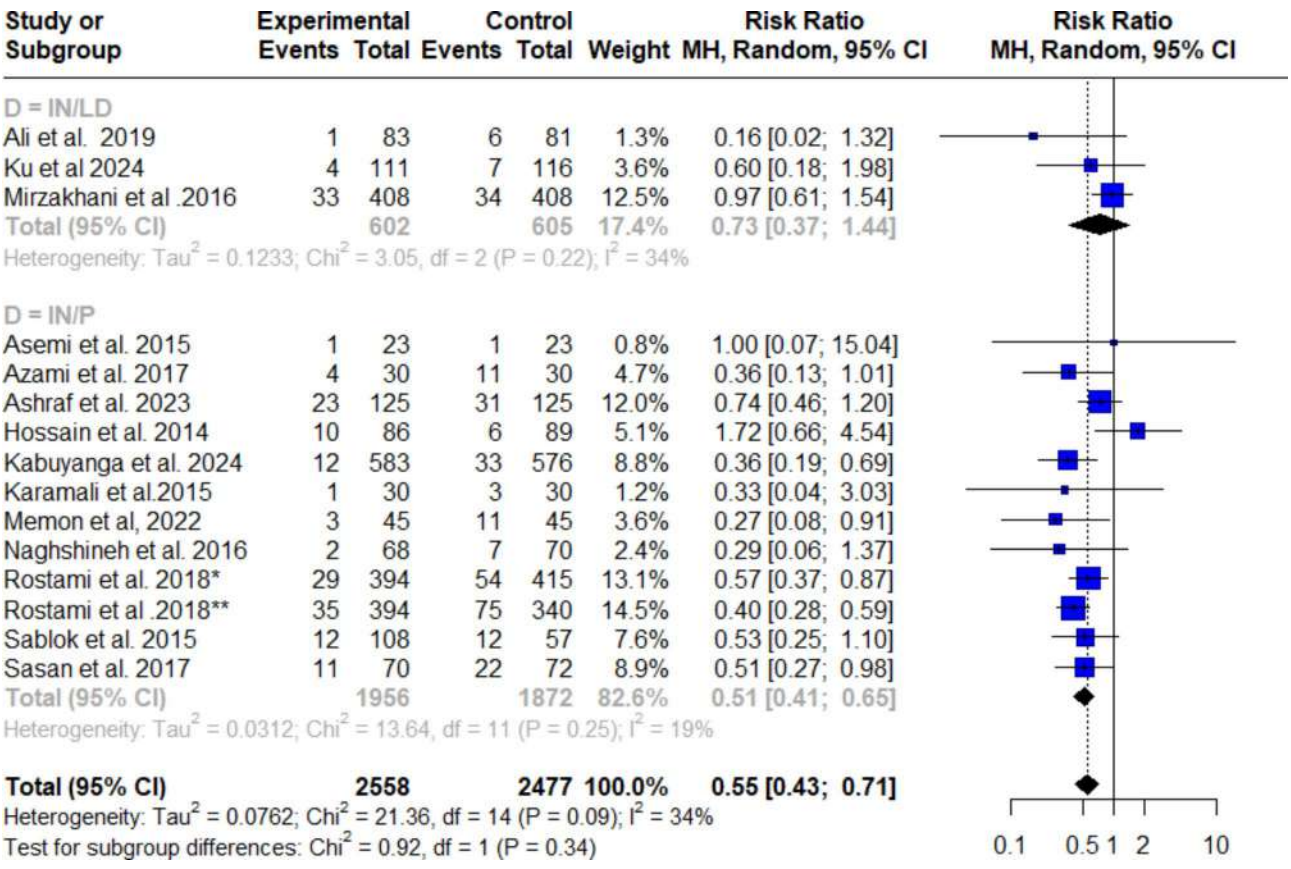

Fig. 3 Incidence of Preeclampsia between Vit. D Supplementation and Control groups. *Moderate deficiency in Vit. D **Severe deficiency in Vit. D. IN/LD: intervention vs. low dose. IN/P: intervention vs. placebo

but also correlated with an average birth weight gain of 302.26 g, alongside the benefits of sun exposure. Adding to the discthisse, Delvin et al. (1986) [48] studied 40 pregnant women at 27 weeks of gestation, revealing that vitamin D supplementation enhanced maternal and neonatal calcium levels, highlighting the critical role of maternal stores for neonatal calcium management. These studies underscore the potential benefits and complexities of vitamin D supplementation during pregnancy.

Publication bias

In agreement with Egger et al. [57], it was applicable to examine potential publication bias in this review via Egger's test for the funnel plot asymmetry, and we found a significant publication bias.

Discussion

Preeclampsia is a pregnancy-specific condition characterized by endothelial dysfunction and vasospasm that typically occurs after 20 weeks of gestation. Clinically, it is defined by the onset of hypertension alongside proteinuria, with or without severe features [58]; the pathogenesis of preeclampsia is not fully understood; however, its development may involve a complex interplay of ischemia and abnormal placentation. These factors can increase the release of angiogenic factors like tyrosine kinase, soluble endoglin, and other pro-inflammatory cytokines such as IL-1β, IL-6, and IL-8, contributing to vascular damage. Emerging evidence suggests that vitamin D plays a crucial role in endothelial repair and angiogenesis, both of which are essential for mitigating the effects of preeclampsia [59]. Additionally, maternal vitamin D deficiency has been associated with an increased risk of cardiovascular diseases and arterial hypertension, suggesting that vitamin D supplementation could serve a protective role in the management of preeclampsia by promoting endothelial health and regulating blood pressure [60]. This meta-analysis integrates the latest studies up to 2024, offering a robust, evidence-based assessment of vitamin D supplementation's impact on preeclampsia and related maternal and fetal outcomes. Through subgroup analyses performed at multiple postoperative time points, we provide a nuanced understanding of the temporal trajectory of these outcomes, evaluating both short-term (e.g., preeclampsia incidence) and long-term (e.g., birth weight, Apgar scores) effects using advanced statistical methods to mitigate heterogeneity and publication bias. Our meta-analysis suggests that vitamin D

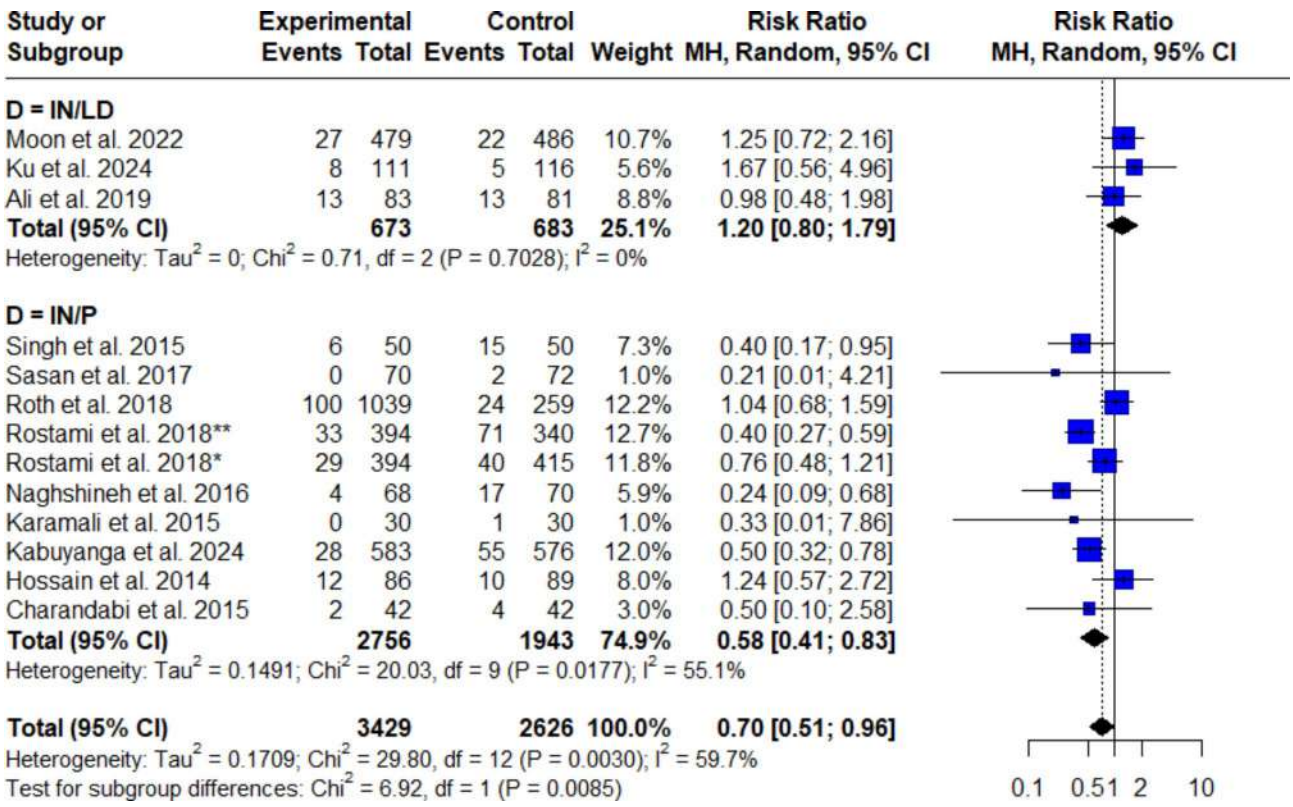

Fig. 4 Incidence of preterm labor between Vit. D supplementation and control groups. *Moderate deficiency in Vit. D **Severe deficiency in Vit. D. IN/LD: intervention vs. low dose. IN/P: intervention vs. placebo

supplementation in early pregnancy can decrease the chances of preeclampsia and provides evidence for the protective role of vitamin D in addressing key maternal and fetal outcomes. This meta-analysis incorporated 33 RCTs that evaluated a range of maternal and fetal outcomes, such as the risk of preeclampsia and preterm labor. Other outcomes assessed were low birth weight, low Apgar scores at 5 min, and 25-OH vitamin D levels. This approach offers several advantages over previous reviews, which predominantly relied on observational studies examining the relationship between vitamin D supplementation during pregnancy and the incidence of preeclampsia. However, the primary focus of this review remains on the incidence of preeclampsia, providing a robust analysis of the potential benefits of vitamin D supplementation during pregnancy. We found that vitamin D supplementation significantly impacted reducing preeclampsia ($P<0.0001$). This reduction was particularly evident in studies where higher doses (≥2000 IU/day) were administered over an extended period. These findings indicate a significant association between vitamin D supplementation and a reduction in the incidence of preterm labor and increased serum 25-OH vitamin D levels ($P<0.01$, $P<0.01$, respectively). On the other hand, we found no significant association between vitamin D supplementation and low birth weight or low Apgar scores at 5 min ($P=0.0568$, $P=0.0571$, respectively).

This study showed a 44% reduction in the risk of preeclampsia with vitamin D supplementation compared to the control group. Additionally, a greater reduction in the risk of preeclampsia was observed when the control group received a placebo (RR [95% CI]=0.5150 [0.40–0.65]) compared to the group that received a low dose of vitamin D (RR [95% CI]=0.73 [0.37–1.43]). However, the test for subgroup differences ($p=0.33$) indicated no statistically significant variation between these groups, emphasizing the benefit of vitamin D supplementation compared to the control group; this is consistent with Azami et al. 2017 [35] A RCT study that concluded that higher doses of vitamin D and other vitamins substantially reduce the risk of preeclampsia. In this study, group A received one Tablet of ferrous sulfate (1 Tablet/day) and one Tablet of Claci-care multimineral vitamin D, which contained 800 mg of calcium, 200 mg of magnesium, 8 mg of zinc, and 400 IU of Vitamin D3/day; group B received only one tablet of ferrous sulfate per day. Specifically, only 4 out of 30 women in Group A, who received higher doses, developed preeclampsia, compared to 10 out of 30 in Group B, who received a lower dose, and 11 out of 30 in the control group. A statistically

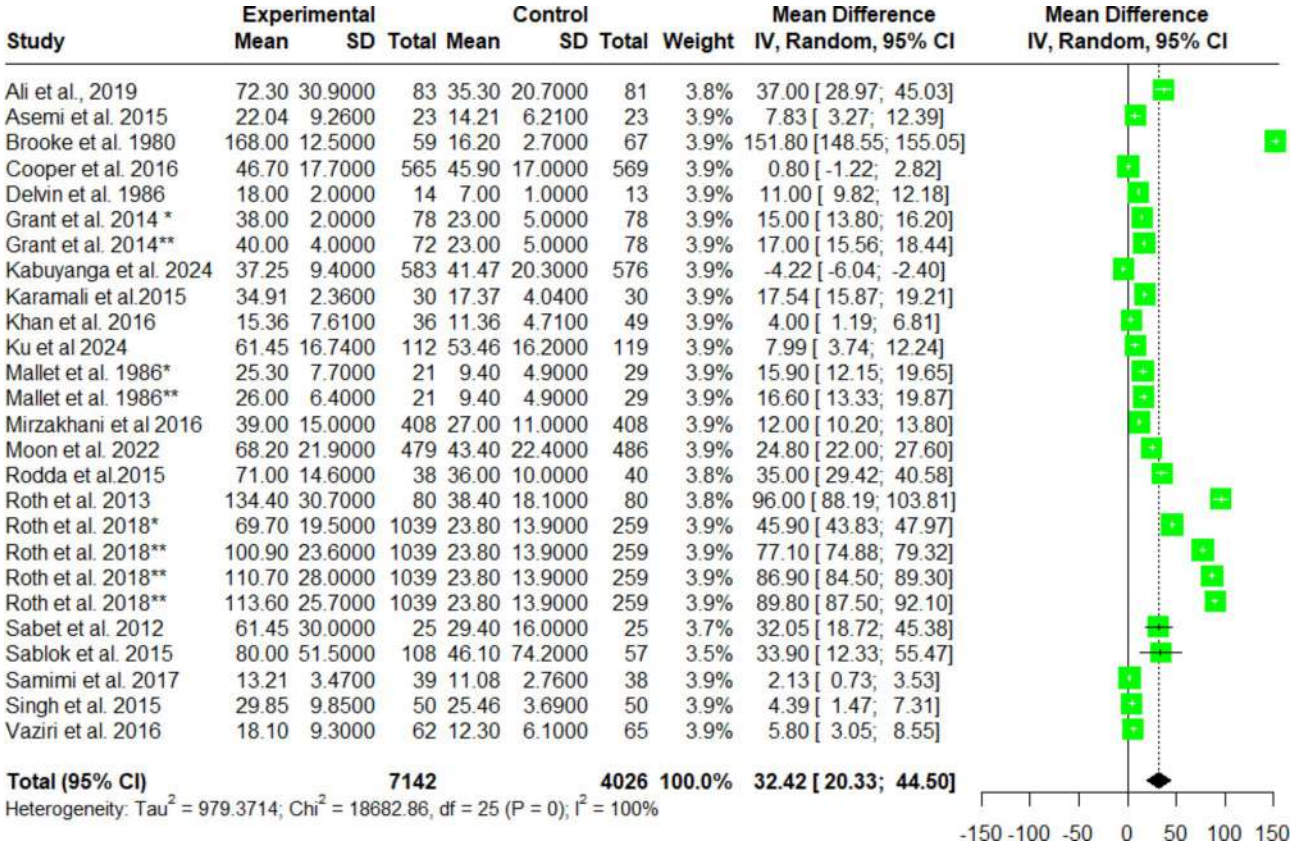

Fig. 5 Measurement of 25-OH between Vit. D supplementation and control groups. * lowest dose for intervention. ** Another group with a higher dose

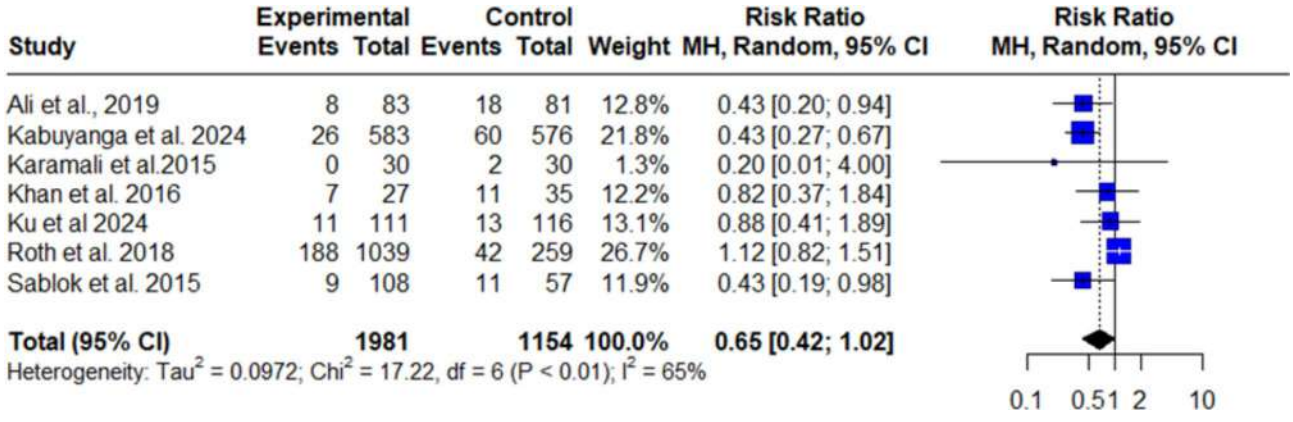

Fig. 6 Low birth weight between Vit. D supplementation and control group

significant p-value of 0.0001; RR [95% CI] = 0.57 [0.45, 0.73)

This result demonstrated a significant association between vitamin D supplementation and a 44.8% reduction in the risk of preterm labor, with a p-value less than 0.0001 and a relative risk of 0.55 (95% CI: 0.42–0.70). Analysis of subgroups that received placebo vs. low-dose vitamin D revealed that the benefit was more pronounced when the control group received a placebo (vitamin D-free) (RR = 0.51, 95% CI: 0.40–0.65) compared to when they received low-dose Vitamin D (RR = 0.7308, 95% CI: 0.37–1.43). Similar to the findings for pre-eclampsia, the difference between subgroups was not statistically significant ($p = 0.3372$). These results suggest that vitamin D supplementation may effectively reduce the risk of preterm labor, with more pronounced effects when compared to a placebo rather than low-dose vitamin D. In contrast to this study, an RCT by Mohammad-Alizadeh-Charandabi et al. 2015 [26] found that supplementation with vitamin D or calcium carbonate had no significant

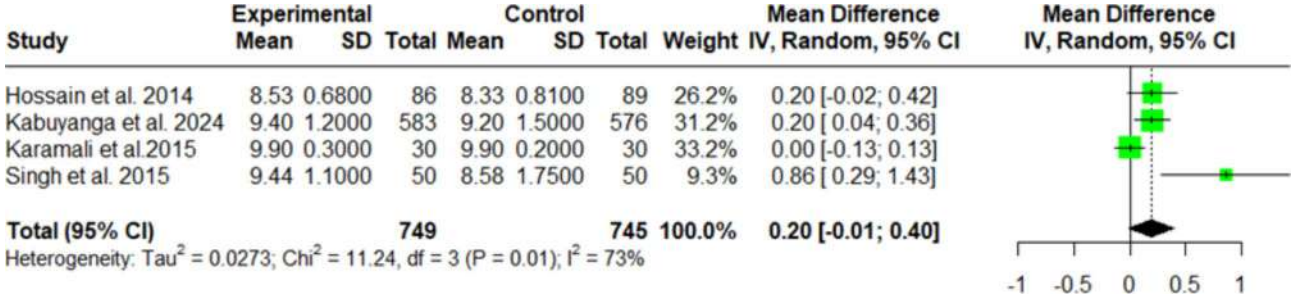

Fig. 7 Low Apgar score at 5 min between Vit. D supplementation and control group

effects on infant anthropometric indices, gestational age, or mode of delivery (RR [95% CI]=0.50 [0.10–2.58]). On the other hand, Singh's study [43] indicated that pregnant women receiving a high dose of 2000 IU of vitamin D daily had a significantly improved mean gestational age of 38.10±2.35 weeks compared to 35.98±3.57 weeks in the control group ($P<0.05$). Additionally, the incidence of preterm birth was significantly lower at 8% ($P=0.001$) among those who achieved sufficient vitamin D levels (>50 nmol/l). These findings support the hypothesis that adequate vitamin D supplementation may reduce the risk of preterm birth, aligning with other studies in this area. According to the findings on the effects of vitamin D on low birth weight and low Apgar scores at 5 min, there were no significant differences observed, with p-values exceeding 0.05 for both measurements. The relative risks reported were RR [95% CI]=0.65 [0.42–1.02] for birth weight and a mean difference of 0.20 [-0.01–0.40] for Apgar scores at 5 min.

Maternal deficiency in 25-hydroxyvitamin D has been linked to an increased proinflammatory response, which can impair vascular health. This study demonstrated a strong association between vitamin D supplementation and increased levels of maternal and cord serum 25(OH) D, with a p-value of 0.0001 and a mean difference of 32.42 [20.33:44.5]. Similarly, Sabet et al. 2012 [54] confirmed that maternal 25-hydroxyvitamin D levels were significantly higher in the supplemented group compared to the control group ($p\leq0.001$). Also, the study by Ali et al. 2019 [36] found a lower incidence of preeclampsia

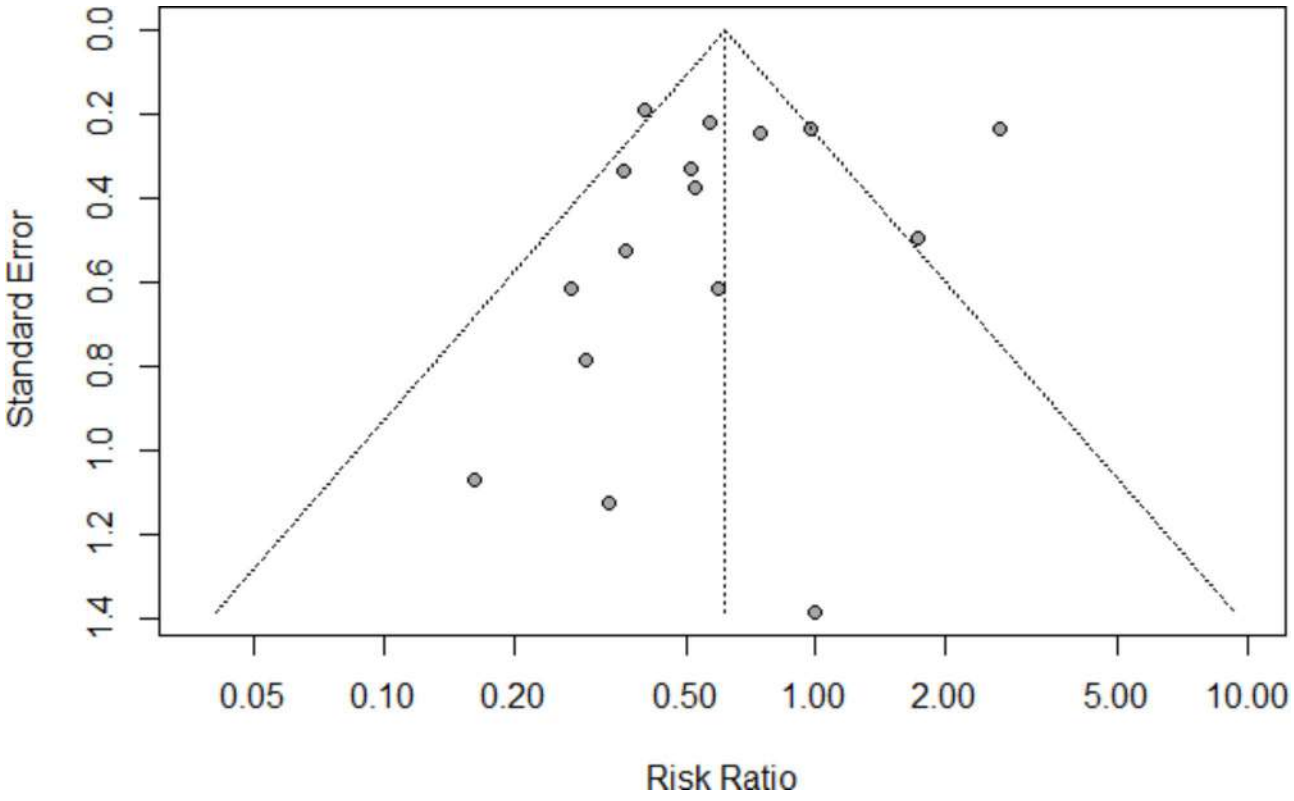

Fig. 8 Publication bias graph

with higher doses of 25-hydroxyvitamin D (4000 IU) compared to a lower dose (400 IU). This suggests that supplementing with higher doses of 25-hydroxyvitamin D, rather than lower doses, may have a positive impact on pregnancy-related issues such as preeclampsia. In this meta-analysis, we found significant publication bias and asymmetry while incorporating the studies and in agreement with Egger et al., [57], using Egger's test for the funnel plot asymmetry (Fig. 8).

Our findings are consistent with and build upon several key studies exploring the role of vitamin D supplementation in reducing preeclampsia risk. Alsubai et al. (2023) highlighted that 25(OH)D deficiency increases preeclampsia risk, with higher doses of vitamin D significantly reducing this risk, a conclusion that aligns with our finding of a 44% reduction in preeclampsia incidence with higher doses (≥2000 IU/day). Similarly, Palacios (2019) observed that vitamin D likely reduces preeclampsia risk and improves serum 25-OH vitamin D levels, which is reflected in our results showing significant increases in maternal and cord serum vitamin D levels. While we did not find significant associations with low birth weight or Apgar scores, our findings on preeclampsia prevention are in line with Purswani et al. (2017), who suggested that vitamin D might mitigate vascular dysfunction through its anti-inflammatory effects. Alanazi et al. (2024) reported a non-significant decrease in preeclampsia risk, contrasting with our robust finding, which may be due to their smaller sample size. Fogacci et al. (2023) and Alimoradi et al. (2024) both confirmed that vitamin D supplementation reduces preeclampsia risk, with Fogacci emphasizing early supplementation, a factor we also found to be important. Overall, our study supports the protective role of vitamin D in preeclampsia prevention, particularly with higher doses, and reinforces the need for further well-designed trials to optimize supplementation strategies and address the effects on other maternal and fetal outcomes [61–66].

Finally, we are recommending the start of screening programs for vitamin D. Deficiency during early pregnancy can help identify women at risk for deficiency and adverse outcomes and how need the supplementation. Supplementing with optimal dosing as higher doses of vitamin D provides a more effective role in preventing pre-eclampsia and preterm labor compared to lower doses.

Conclusion

This systematic review and meta-analysis demonstrate the potential benefits of vitamin D supplementation in reducing the risk of preeclampsia and preterm labor among pregnant women, with findings showing a 43% reduction in preeclampsia risk and a 30% decrease in preterm labor. These outcomes suggest that vitamin D may play a role in supporting vascular function, reducing inflammation, and enhancing placental development during pregnancy. While maternal outcomes showed clear improvement, neonatal outcomes such as low birth weight and Apgar scores at 5 min did not exhibit significant changes, indicating a selective influence of vitamin D on maternal health. The consistent increase in maternal serum vitamin D levels in the supplemented group underscores the effectiveness of supplementation in addressing deficiencies. Future research should aim to optimize dosing regimens, evaluate long-term health impacts for both mother and child, and clarify the mechanisms by which vitamin D exerts its protective effects, ultimately guiding clinical guidelines and improving prenatal care practices.

Abbreviations

RCTs	Randomized Control Trials
APGAR	Appearance, Pulse, Grimace
RR	Risk ration
MD	Mean Difference
CI	Confidence Interval
HELLP	Hemolysis, Elevated liver enzymes, and Elevated Platelets
PRISMA	Preferred Reporting for systematic review and meta-analysis
DBP	Diastolic Blood Pressure
SBP	Systolic Blood Pressure
BMI	Body Mass Index
ROB-2	Risk of Bias
IQR	Interquartile Range
SMD	Standard Mean Difference
X^2	Chi-square
I^2	I square
IU	International Unit
IL	Interleukin
GDM	Gestational Diabetic mellitus
ARDS	Acute respiratory Distress syndrome

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Author contributions

K.M; T.I.G; I.S; A.A: conceptualization and methodology; M.R; S.M.M: Investigation and data curation; K.M; I.S; A.M.M; S.K; K.E: formal analysis; I.S; K.M; M.S; A.I.D; A.E: Writing - Original Draft.: A.A: Supervision; K.M; T.I.G: Project administration; I.S; M.I: Writing - Review & Editing. I.S: Correspondence. All authors read and approved the final content.

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Data availability

All data generated or analyzed during this study are included in this published article.

Declarations

Ethical approval

Not applicable.

Consent to Publish

Not applicable.

Competing interests

The authors declare no competing interests.

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