Effect of Vitamin D Supplementation during Pregnancy on Maternal and Neonatal Outcomes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials

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Objective: To assess the effects of vitamin D supplementation during pregnancy on obstetric outcomes and birth variables.
Design: Systematic review and meta-analysis of randomized controlled trials (RCTs).
Setting: Not applicable.
Patient(s): Pregnant women and neonates.
Intervention(s): PubMed and 5 other research databases were searched through March 2014 for RCTs evaluating vitamin D supplementation ± calcium/vitamins/ferrous sulfate vs. a control (placebo or active) during pregnancy.
Main Outcome Measure(s): Measures were: circulating 25-hydroxyvitamin D [25(OH)D] levels, preeclampsia, gestational diabetes mellitus (GDM), small for gestational age (SGA), low birth weight, preterm birth, birth weight, birth length, cesarean section. Mantel-Haenszel fixed-effects models were used, owing to expected scarcity of outcomes. Effects were reported as relative risks and their 95% confidence intervals (CIs).
Result(s): Thirteen RCTs (n = 2,299) were selected. Circulating 25(OH)D levels were significantly higher at term, compared with the control group (mean difference: 66.5 nmol/L, 95% CI 66.2–66.7). Birth weight and birth length were significantly greater for neonates in the vitamin D group; mean difference: 107.6 g (95% CI 59.9–155.3 g) and 0.3 cm (95% CI 0.10–0.41 cm), respectively. Incidence of preeclampsia, GDM, SGA, low birth weight, preterm birth, and cesarean section were not influenced by vitamin D supplementation. Across RCTs, the doses and types of vitamin D supplements, gestational age at first administration, and outcomes were heterogeneous.
Conclusion(s): Vitamin D supplementation during pregnancy was associated with increased circulating 25(OH)D levels, birth weight, and birth length, and was not associated with other maternal and neonatal outcomes. Larger, better-designed RCTs evaluating clinically relevant outcomes are necessary to reach a definitive conclusion. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Vitamin D, pregnancy, maternal outcomes, neonatal outcomes, meta-analysis

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Vitamin D is an established fundamental nutritional factor responsible for regulation of bone metabolism, absorption of calcium and phosphate, and maintenance of muscle function. Observational studies suggest that vitamin D is essential for many physiologic processes;

thus, adequate levels are necessary and advantageous for optimal health (1–3). Despite its vitamin designation, cholecalciferol, or vitamin D_3, can be synthesized by mammals from 7-dehydrocholesterol, via appropriate exposure to sunlight. Cholecalciferol and ergocalciferol (vitamin D_2) can be obtained from the diet as well. In humans, both cholecalciferol and ergocalciferol are sequentially transformed into 25-hydroxyvitamin D_3 [25(OH)D], 25-hydroxycholecalciferol, or calcidiol, in the liver, which are subsequently transformed in kidneys and other tissues into 1,25-dihydroxyvitamin D_3 [1,25(OH)2D], 1,25-dihydroxycholecalciferol or calcitriol (1–3).

Sufficient vitamin D concentrations are needed during pregnancy to address the increasing demand for calcium, by the fetus, during its growth and development (3, 4). Pregnant women who did not receive vitamin D supplementation showed a reduction in circulating 25(OH)D levels during the third trimester compared with the first trimester (4, 5). Several observational studies have reported that low maternal circulating 25(OH)D concentrations in pregnant women may have negative health consequences for both mothers and newborns (3, 6). Studies have suggested that lower levels of circulating 25(OH)D are associated with risks of recurrent pregnancy losses, preeclampsia, gestational diabetes, maternal infections, preterm birth, small-for-gestational-age (SGA) infants, and poor offspring health (3, 6, 7).

Vitamin D supplementation may increase serum vitamin D levels in both mothers and infants (8, 9). However, what remains to be determined is whether vitamin D supplementation is protective against maternal morbid conditions, SGA, or intrauterine growth restriction, and whether it improves neonatal health. Findings from observational studies have been inconclusive, owing to the heterogeneity of the dose and duration of supplementation, the timing of supplementation initiation, maternal factors (overweight and obesity, general health before pregnancy), and measured endpoints.

The effects of vitamin D supplementation on maternal and neonatal outcomes in randomized controlled trials (RCTs) have been previously examined in 3 systematic reviews and/or meta-analyses (7, 9, 10). These studies had several limitations, including deficiencies in study design (inclusion of quasi-randomized trials and observational studies), and are restricted by the outcomes evaluated. In addition, more RCTs have been published since the publication of the last meta-analysis. The current comprehensive systematic review and meta-analysis of RCTs includes studies published more recently. We evaluated current evidence on the effects of vitamin D supplementation during pregnancy on several maternal and neonatal endpoints. Clinical relevance of these findings and their potential translational clinical applications are discussed.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11). Formal institutional review board approval was not required because this analysis pools published study data.

Literature Search

PubMed-Medline, EMBASE, Scopus, Web of Science, Cochrane Library, and www.clinicaltrials.gov were searched. A basic search strategy was developed for PubMed, and modified as needed for other databases; a search strategy was devised for each outcome (Supplemental Table 1, available online). The search time parameters were from inception of each database through March 2014. The language in which studies were written was not used to restrict selection, but only human studies were selected. References from the selected articles, including relevant review papers, were reviewed to identify all relevant studies.

Inclusion and Exclusion Criteria

The meta-analysis evaluated vitamin D supplementation, used alone and in combination with calcium and vitamin supplements, on pregnancy outcomes. Randomized controlled trials of pregnant women of any gestational or chronologic age and parity, without previous disease history, were included. Interventions of interest were: vitamin D alone vs. no treatment (placebo); vitamin D + calcium vs. no treatment (placebo); and vitamin D + calcium vs. calcium. Vitamins and ferrous sulfate were allowed in both trial arms. Controls of interest were: active controls, usual treatment without active control, and placebo.

In an RCT (8), all women received a standard prenatal multivitamin containing 400 international units (IU) of vitamin D_3. In addition, all women received a vitamin D_3 supplement of 0 IU (placebo), 1,600 IU, or 3,600 IU of vitamin D_3, for a total of 400 IU, 2,000 IU, and 4,000 IU of vitamin D supplementation, respectively (Table 1). Exclusion criteria were: (1) no appropriate control group; (2) data were not available or could not be extracted for the study groups; and (3) multiple pregnancies.

Prespecified Primary Outcomes

Maternal primary outcomes were: preeclampsia (as defined by trialist); gestational diabetes (as defined by trialist); and vitamin D status at term (25-hydroxyvitamin D in nmol/L). Neonatal primary outcomes were: intrauterine growth restriction (as defined by trialist); low birth weight (<2,500 g); premature birth (<37 weeks of gestation); and birth weight in grams.

Prespecified Secondary Outcomes

Maternal secondary outcomes were: cesarean section and maternal mortality (death while pregnant or within 42 days of termination of pregnancy). Neonatal secondary outcomes were: birth length (cm); Apgar score of <7 at 5 minutes; stillbirth (as defined by trialist); neonatal infection (within 28 days after delivery); very low birth weight (<1,500 g); early preterm birth (<34 weeks gestation); and neonatal mortality (within 28 days after delivery).

Study Selection and Data Extraction

For this review, 2 sets of investigators independently reviewed titles and abstracts for eligibility. Disagreements regarding

TABLE 1

Characteristics of included studies in a systematic review and meta-analysis of randomized controlled trials to evaluate the effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes.

First author, year published	Study location	Source of funding	No. of participants	Age (y), mean (SD)	Treatment group	Dosage	Treatment duration (wk)	25-OHD quantification method	Gestational age at sampling (wk)	Primary endpoint
Asemi (14), 2013	Iran	University grant	27	24.8 (3.6)	Placebo		9	ELISA	25	C-reactive protein
			27	25.3 (4.2)	25(OH)D	400				
Brooke (15), 1980	United Kingdom	Hospital funds; government	67	23.7 (3.1)	Placebo		8–12	Protein-binding assay	28–32	Maternal and infant calcium homeostasis, fetal growth
			59	23.9 (4.8)	Vitamin D_2	1,000				
Delvin (16), 1986	France	Government; private funds	20	NA	No intervention		12	Radioligand assay	26–27	Maternal and neonatal calcium homeostasis
			20		Vitamin D_3	1,000				
Goldring (17), 2013	United Kingdom	Private foundation	60	37.9 (36.9–39.9)	No intervention		13	RIA	27	Wheeze prevalence
			60	37.1 (36.5–38.8)	Vitamin D_2	800				
			60	37.4 (36.5–39.5)	Vitamin D_3	200,000 IU bolus				
Hashemipour (18), 2014	Iran	University funds	65	27.6 (4.6)	Elemental Ca + MVI	200 mg/d	8	ELISA	24–26	Newborn length at birth
			65	27.0 (4.6)	Elemental Ca + MVI + Vitamin D_3	50,000 IU/wk				
Hollis (8), 2011	United States	University funds; government	166	27.0 (5.6)	Placebo + MVI-400		24–28	RIA	12–16	Maternal and neonatal 25-OHD at delivery
			167	27.4 (5.7)	MVI-400 + Vitamin D_3	1,600				
			169	26.6 (5.4)	MVI-400 + Vitamin D_3	3,600				
Hossain (19), 2014	Pakistan	Government	100	25.2 (4.4)	$Feso_4$ + calcium lactate	200/600 mg/d	20	Chemiluminescence immunoassay	20	Neonatal Vitamin D status, obstetric outcomes, neonatal growth and Apgar scores
			100	26.0 (3.1)	$FeSo_4$ + calcium lactate + Vitamin D_3	4,000				
Mallet (20), 1986	France	NA	29	25 (18–35)	No intervention		12	Protein-binding assay	NA	Maternal and cord blood 25(OH)D, 1,25 (OH)2D
			21	26 (18–35)	Vitamin D_2	1,000 IU/d				
			27	25 (19–36)	Vitamin D_2	200,000 IU single dose				
Marya (21), 1987	India	NA	200	20–35	No intervention		16–20	NA	NA	Blood pressure
			200	20–35	Ca + Vitamin D	375 mg/1,200 IU/d				
Marya (22), 1988	India	NA	100	24.1 (3.2)	No intervention		12	NA	NA	Maternal and cord sera biochemical parameters, fetal birth weight. and anthropometry
			100	24.0 (3.7)	Vitamin D_3	600,000 IU, 2 doses				
Roth (23), 2013	Bangladesh	Private foundation	80	22.4 (3.4)	Placebo		12	High-performance liquid chromatography tandem mass spectroscopy	27.9 (mean)	Maternal and neonatal 25(OH)D, maternal serum calcium
			80	22.4 (3.5)	Vitamin D_3	35,000 IU/wk				

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TABLE 1

Continued.

First author, year published	Study location	Source of funding	No. of participants	Age (y), mean (SD)	Treatment group	Dosage	Treatment duration (wk)	25-OHD quantification method	Gestational age at sampling (wk)	Primary endpoint
Sabet (24), 2012	Iran	University funds	25	26.0 (6.2)	Placebo		12	ELISA	28	Maternal and cord blood 25-OHD and intact parathyroid hormone
			25	26.6 (4.7)	Vitamin D_3	100,000 IU/mo				
Yu (25), 2009	United Kingdom	University funds	60	NA	No intervention		13	NA	27	Maternal and cord blood 25-OHD at delivery
			60		Vitamin D_2	800				
			60		Vitamin D_2	200,000 IU bolus				

Note: Dosage is IU per day, unless otherwise indicated. Age for Goldring is given as median (IQR); for Mallet as mean (range); and for Marya as range. ELISA = enzyme-linked immunosorbent assay; $FeSo_4$ = ferrous sulfate; IQR = interquartile range; IU = international units; MVI = multivitamin; MVI-400 = multivitamin containing 400 IU; NA = not available; RIA = radioimmunoassay; 25(OH)D = 25-hydroxyvitamin D_3; 25-OHD = 25-hydroxyvitamin D_3; 1,25 (OH)2D = 1,25-dihydroxyvitamin D.

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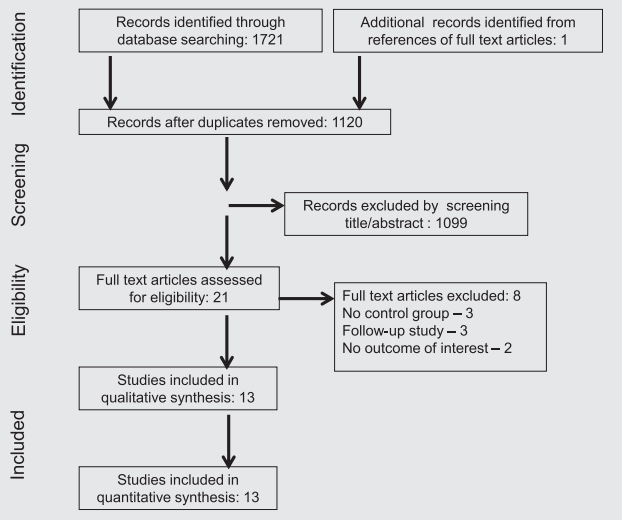
FIGURE 1



Flow diagram of selected studies.

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abstract selection were resolved by consensus or discussion with another investigator not in the first 2 groups. The study selection flow chart was created according to PRISMA guidelines (11).

The 2 sets of investigators independently extracted relevant data (participants, specific vitamin D intervention, and outcome characteristics) from each full-text article and recorded the data directly onto previously designed data-extraction spreadsheets. Entries were compared for accuracy, and any discrepancies were resolved by consensus or discussion with another investigator not in the first 2 groups, if needed.

Authors of original studies were contacted if necessary for unpublished information relevant to the study. In cases of duplicate publications or multiple reports of the primary study, data extraction was optimized by using the best information available for all items from the same study. The longest follow-up period associated with primary or secondary outcomes was used.

Risk of Bias Assessment in Randomized Controlled Trials

Two sets of investigators independently evaluated the risk of bias from each eligible RCT. Any discrepancies were resolved by consensus or discussion with another investigator. The Cochrane Collaboration tool for assessing risk of bias in RCTs was used (12). The following items were evaluated: generation of the allocation sequence (selection bias); concealment of the allocation sequence (selection bias); blinding (detection and performance bias); blinding of participants and personnel to outcome assessment; incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other biases. For each RCT, each item was described as having either a low risk of bias, a high risk of bias, or an unclear risk of bias.

TABLE 2

Assessment of bias risk of randomized clinical trials included in a systematic review and meta-analysis to evaluate the effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes.

First author, year published	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Asemi (15), 2013	Low	Low	Low	Low	Low	Low	Low
Brooke (16), 1980	Unclear	Unclear	Low	Unclear	Low	Low	Low
Delvin (17), 1986	Unclear	Unclear	Low	Unclear	Low	Low	Low
Goldring (18), 2013	Low	Low	Low	Low	Low	Low	Low
Hashemipour (19), 2014	Low	Unclear	High	Unclear	Low	Low	Low
Hollis (8), 2011	Low	Unclear	Low	Low	Low	Low	Low
Hossain (20), 2014	High	Unclear	High	Unclear	Low	Low	Low
Mallet (21), 1986	Low	Unclear	Unclear	Low	Low	Low	Low
Marya (22), 1987	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Marya (23), 1988	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Roth (24), 2013	Low	Low	Low	Low	Low	Low	Low
Sabet (25), 2012	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Yu (26), 2009	Low	High	High	Unclear	Low	Low	Low

Note: Bias risk was determined according to the Cochrane risk of bias tool (12), using the following questions by category. Sequence generation: Was the allocation sequence adequately generated? Allocation concealment: Was allocation adequately concealed? Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented during the study? Incomplete outcome data and withdrawals: Were intention-to-treat analyses performed? Had participants withdrawn from the study? Selective outcome reporting: Free of selective reporting? Other sources of bias: Was sample size calculated? Were inclusion and exclusion criteria and baseline characteristics defined? Were conflicts of interest reported?

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Statistical Analysis

For analyses, fixed-effects models and the Mantel-Haenszel method were used, owing to an anticipated scarcity of events (<10% of the total number of individuals in an arm). This method has better statistical properties than the inverse variance method when events are few; in particular, estimates of the standard errors of the effect estimates that are used with the this method may be poor (13). Outcomes data available in ≥3 studies were meta-analyzed.

Associations were reported as relative risks (RRs) and their 95% confidence intervals (CIs). Heterogeneity was tested with the Cochrane χ^2 test, and the degree of heterogeneity was quantified with the I^2 statistic and its 95% CI. An I^2 value between 30% and 60% was described as moderate heterogeneity. Publication bias was assessed with the funnel plots and formally tested with the Egger's test. If enough information was available, we planned to perform subgroup analyses by level of vitamin D at the beginning of pregnancy (normal vs. abnormal), and by Cochrane's risk-of-bias level. If vitamin D levels were provided in ng/mL, values were converted using the formula: 1 ng/mL = 2.5 nmol/L. All analyses were done with RevMan 5.1 (14) and the package *metafor* of R 3.0.1 (www.r-project.org).

RESULTS

General Characteristics of Studies

After the evaluation of 1,120 abstracts from primary and secondary sources, 1,099 were excluded; 21 were assessed from the full text. From these, 8 studies were excluded (Fig. 1). Thus, 13 RCTs (n = 2,299) were included in this systematic review. All were published between 1980 and 2014, were conducted in both developing and developed countries, and had sample sizes in the range 40–400 pregnant women, most age <30 years (8, 15–26) (Table 1). From the total of 13 RCTs, 3–8 were included in the various meta-analyses, depending on the health outcome studied.

Vitamin D_2 or D_3, alone or in combination with multivitamins, calcium, or iron were the interventions; the controls were active, placebo, or no intervention. In 1 RCT (8), all women received a standard prenatal multivitamin containing 400 IU of vitamin D_3, and an additional vitamin D_3 supplement of either 0 IU (placebo), 1,600 IU, or 3,600 IU, for totals of 400 IU, 2,000 IU, and 4,000 IU of vitamin D supplementation, respectively (Table 1). The duration of the vitamin D intervention was 8–28 weeks of gestation.

Outcomes were heterogeneous, and the most frequently reported outcomes were maternal and neonatal 25(OH)D levels at delivery. Vitamin D levels were measured mainly by using competitive binding assays: an enzyme-linked immunosorbent assay in 3 RCTs, protein-binding assays in 2, a radioimmunoassay in 2, a radioligand assay in 1, and a chemiluminescence assay in 1, Measures were either not stated or not available in 3 RCTs. In 1 study, measurement was done using high-performance liquid chromatography (Table 1).

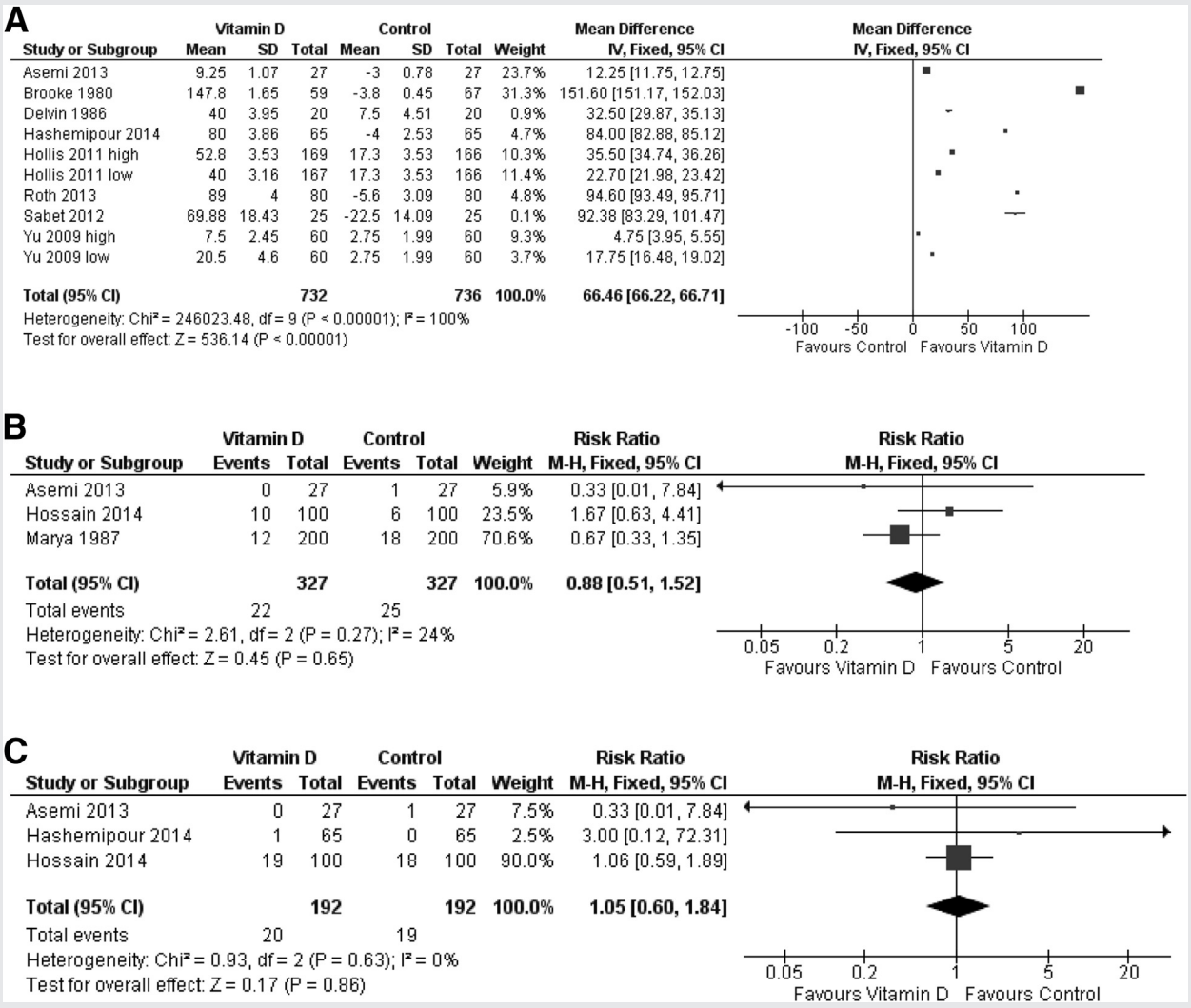
Risk-of-Bias Assessment

Risk-of-bias assessment is shown in Table 2. Of the 13 included studies, 3 had a low risk of bias, 2 had a high risk of bias, and the remaining 8 had an unclear risk of bias.

Meta-Analyses of Primary Outcomes

As expected, the 25(OH)D levels at delivery were higher in women who received the intervention vs. those in the control group (mean difference: 66.5 nmol/L, 95% CI 66.2–66.7) (Fig. 2A). Incidences of preeclampsia and gestational diabetes were similar in women with vs. without the vitamin D intervention (RR 0.88, 95% CI 0.51–1.52; and RR 1.05, 95% CI 0.60–1.84, respectively) (Fig. 2B and 2C).

FIGURE 2



Meta-analyses of the effect of vitamin D intervention on primary outcomes (**A**) circulating 25-OHD; (**B**) preeclampsia; (**C**) gestational diabetes; (**D**) small for gestational age; (**E**) low birth weight; (**F**) preterm birth; (**G**) birth weight, and secondary outcomes (**H**) birth length; and (**I**) cesarean section. CI = confidence interval; D2 = supplement of vitamin D2; D3 = supplement of vitamin D3; df = degrees of freedom; high = higher dose; low = lower dose; M-H = Mantel-Haenszel; 25(OH)D = 25-hydroxyvitamin D_3.

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In contrast with the control group, incidences of SGA (RR 0.78, 95% CI 0.50–1.21), low birth weight (RR 0.72, 95% CI 0.44–1.16), and preterm birth (RR 1.26, 95% CI 0.60–2.63) in neonates were not different for the vitamin D intervention groups (Fig. 2D–2F). Birth weight was slightly but significantly greater for the vitamin D groups (mean difference: 108 g, 95% CI 60–155 g) (Fig. 2G).

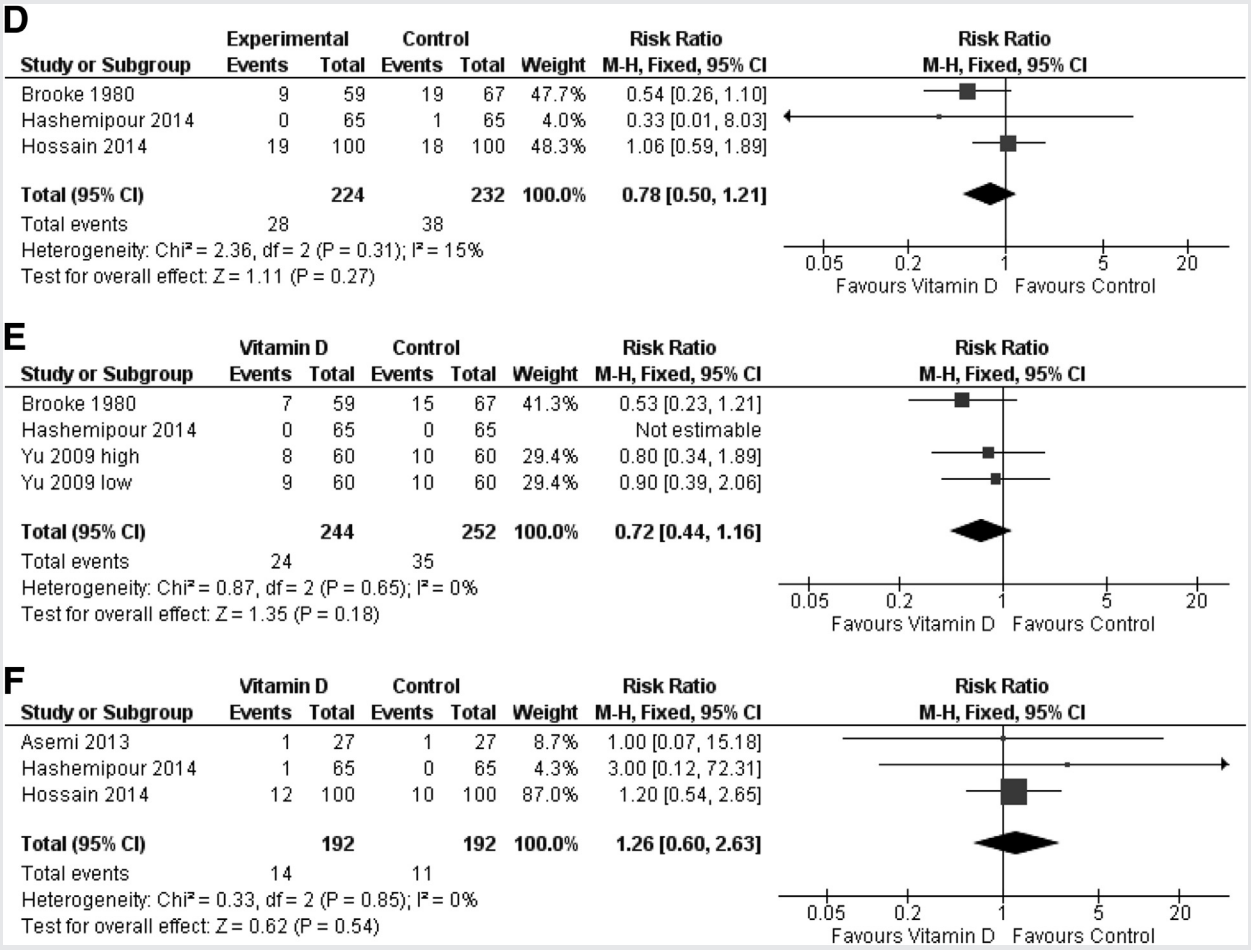
Meta-Analyses of Secondary Outcomes

Neonatal birth length was slightly but significantly greater in the vitamin D intervention group (mean difference: 0.3 cm, 95% CI 0.19–0.41) (Fig. 2H). The incidence of cesarean section was not different between groups (RR 0.94, 95% CI 0.78–1.13) (Fig. 2I). Other prespecified secondary outcomes were not reported in ≥3 studies and thus were not meta-analyzed. The prespecified subgroup analyses were not conducted, owing to the scarcity of studies providing relevant information.

DISCUSSION

This systematic review and meta-analysis of RCTs showed a significant increase in circulating 25(OH)D in pregnant women who received vitamin D supplementation. Birth weight and birth length were slightly but significantly greater in the neonates of mothers who received vitamin D supplements, compared with those who did not. In addition, the current investigation found that the incidence of preeclampsia, gestational diabetes, preterm birth, SGA, and cesarean section were similar among pregnant women who did, vs. did not, receive vitamin D supplementation.

FIGURE 2 Continued



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Vitamin D Supplementation and Fetal Birth Weight and Length

Although the improvements in birth weight (found in 8 RCTs) and length (found in 6 RCTs) were rather small, they suggest indirectly that vitamin D supplementation exerts a positive effect on fetal cell mass and function, skeletal mineralization, and metabolism (27). On the other hand, small differences in gestational age could be contributing to the effect (28). The small effects on birth size seem less likely to be a function of growth restriction (both the SGA estimate and the low birth weight point estimates are lower, but not significantly, for those in the vitamin D supplementation group) than of the gestational age distribution, because the preterm estimate is slightly elevated, though again, not significantly so.

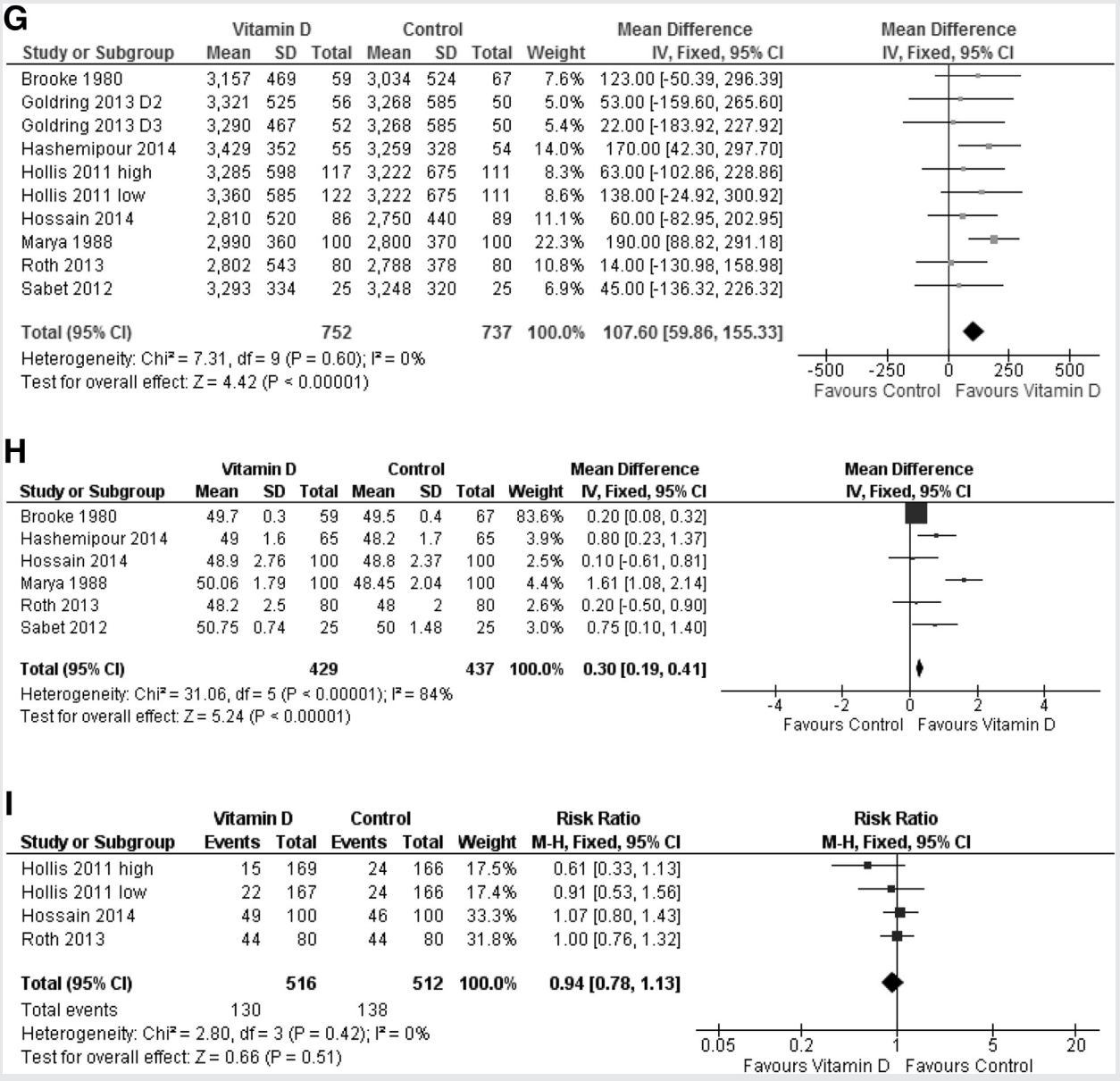
In any case, fetal growth is a complex process dependent on many factors, including genetic background, birth interval, trophoblast implantation, placental development, nutrition, and physical activity (29–31). Thus, vitamin D may play a minor role in fetal growth, compared with other factors. Future research should be based on more-standardized growth-assessment procedures (32), to control for some of the limitations found in the available evidence.

Vitamin D Supplementation and Low Fetal Birth Weight, Small for Gestational Age, and Preterm Birth

An inverse correlation of cord blood 25(OH)D levels at delivery and birth weight has been reported (8), whereas other studies have shown that newborns of mothers with severe vitamin D deficiency had shorter birth length, and smaller head circumference and birth weight (33). In the current meta-analysis, including 4 RCTs, vitamin D supplementation did not prevent the risk of low birth weight (<2,500 g). Pooled data from 3 RCTs in this study showed no significant effect of vitamin D supplementation on the risk of SGA.

Reports are conflicting on the role of vitamin D and the risk of preterm birth. Premature amniotic membrane rupture and preterm delivery have been associated with vitamin D deficiency and inflammatory response (34, 35), although

FIGURE 2 Continued



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other studies did not confirm an association between 25(OH)D status and preterm birth (36, 37). Pooled analysis of 4 RCTs in the current study showed no significant effect of vitamin D supplementation on prevention of preterm birth. Some recent publications have reported alterations in the cervicovaginal fluid content of vitamin D and vitamin D binding protein (VDBP) as biomarkers of vaginal inflammation and preterm birth risk several weeks before delivery (38). Future research on vitamin D supplementation and preterm birth should include the study of cervicovaginal VDBP and serum 1,25(OH)2D, along with 25(OH)D, to monitor the response to various doses of vitamin D supplements.

Vitamin D Supplementation and Preeclampsia

Controversy remains regarding the clinical and epidemiologic evidence on the relationship between low maternal vitamin D levels and the risk of preeclampsia (39, 40). In the current meta-analysis, 3 RCTs assessed vitamin D supplementation and preeclampsia risk and did not find any significant association between them. However, placenta dysfunction has a major pathogenetic role on preeclampsia development, and the increased oxidative stress produces various vitamin D–related alterations (expression of VDBP, 25-hydroxylase, 1a-hydroxylase, and vitamin D receptor) (41). On the other hand, 1 RCT (20) included in our

meta-analysis used a combination of vitamin D, ferrous sulfate (200 mg), given twice daily, and 600 mg of calcium lactate daily for the treatment group, vs. ferrous sulfate and calcium in the control group. The other two studies (15, 22) used vitamin D in the treatment group, vs. placebo. The results from the Hossain et al. study (20) study seem to have driven the overall RR toward the null. Some studies suggest that calcium supplementation reduces preeclampsia risk (42, 43).

Vitamin D Supplementation and Gestational Diabetes Mellitus

Low vitamin D levels have been associated with altered glucose homeostasis in both in vitro and observational studies (44–46). In the current meta-analysis of 3 RCTs that included a small number of women overall, no significant benefit of vitamin D supplementation was found in relation to risk of gestational diabetes. However, several confounding factors have not been controlled for in the available data. Excessive weight gain during pregnancy contributes to both the risk of gestational diabetes and low maternal vitamin D levels, as this vitamin is fat soluble and migrates from the blood to fat tissue (47). In addition, higher levels of VDBP in obese patients are associated with a reduced fraction of the bioactive, unbound 15(OH)D (48).

Vitamin D Supplementation and Cesarean Section

Low circulating blood 25(OH)D levels have been reported to be associated with an increased rate of cesarean section (49, 50). On the contrary, first-trimester maternal vitamin D levels were similar in women who subsequently have a vaginal delivery vs. those who deliver by elective or emergency cesarean section (51). In the current study, 4 RCTs were pooled; no significant effect was found of vitamin D supplementation on cesarean section rates. Cesarean section indications are quite variable, owing to many factors relating to the obstetric experience, hospital facilities, and other issues that are very difficult to control.

Limitations of Previous Meta-Analyses

De Regil et al. (9), in an evaluation of RCTs and quasi-randomized trials, found that vitamin D supplementation was not associated with preeclampsia or low birth weight. Thorne-Lyman and Fawzi (7) evaluated observational studies and RCTs and found an association of vitamin D supplementation and diet, with a lower incidence of low birth weight; other outcomes were not significantly affected by the interventions. Finally, Harvey et al. (10) assessed observational studies and RCTs for the effect of serum vitamin D levels, or supplementation of women with vitamin D or food containing vitamin D on maternal and neonatal outcomes. In comparison with these 3 earlier systematic reviews (Supplemental Table 2, available online), the current meta-analysis predefined several other relevant maternal and neonatal outcomes, excluded observational studies that were prone to several biases, and included a larger number of RCTs and time spans ranging to as recently as 2014.

Limitations of Current Meta-Analyses

This systematic review has several limitations. The available studies were heterogeneous in terms of dose, type, and duration of vitamin D supplementation, as well as maternal and neonatal endpoints. In addition, serum 25(OH)D levels were quantified using various types of competitive binding assays, with only 1 RCT using high-performance liquid chromatography, the gold standard of measurement. Competitive binding assays were the most-often used method of assessing 25(OH)D. These methods, compared with high-performance liquid chromatography, underestimate serum levels, owing to differences in affinity between the antibodies or binding elements used (52, 53).

Methodologic deficiencies are an additional limitation; a few RCTs initiated supplementation in the second half of pregnancy, and many clinical conditions (e.g., preeclampsia and gestational diabetes) cannot be prevented as the several biochemical, metabolic, and vascular changes have already been made. In addition, definitions of some clinical outcomes varied among included studies. Given that many studies were carried out in developing countries, the possibility of maternal and child undernutrition in the studied population cannot be ruled out (54). In such cases, the small contribution of vitamin D supplementation would not be potent enough to neutralize the basal nutritional status.

Other confounding factors not assessed in available RCTs include diet, vitamin D content, seasonality, body weight gain during pregnancy, ethnicity, and skin characteristics (3, 4, 6, 39, 53, 55). Birth spacing was not reported in the RCTs, and therefore we could not control for this factor. Most of the included studies had an unclear risk of bias, according to the Cochrane Risk of Bias Tool.

Recognizing the limitations of studies included in meta-analyses may stimulate future studies with better design and methods that will improve available evidence and definitively define the role of vitamin D in pregnancy and neonatal health. Future RCTs should consider initiating vitamin D supplementation early in pregnancy or even before pregnancy, controlling for confounding factors, using higher and more-sustained doses than those studied so far, with more-objective endpoints (e.g., ultrasound assessment and serial measurement of biochemical markers) (31, 54–56).

Finally, a remaining issue is whether a linear correlation exists between vitamin D supplementation and maternal and neonatal outcomes, and whether various obstetric endpoints have varying cutoffs. Some experimental and clinical studies suggest that hypervitaminosis D may have negative effects on obstetrics endpoints (57, 58). Thus, the possibility that some outcomes could have U-shaped associations, with risks at both low and high levels, cannot be disregarded (59). However, vitamin D supplementation of up to 4,000 IU per day seemed to be safe during pregnancy (8, 20).

The current state of the evidence is controversial for some other endpoints, and the actual benefit of vitamin D supplementation in pregnancy remains unclear. Additional longitudinal studies may clarify the actual impact of vitamin D deficiency during pregnancy. Randomized trials are required to define the benefits of vitamin D supplementation

in reducing the incidence of adverse outcomes in mothers and infants. Fulfilling at least the recommended dietary allowance of 600 IU per day seems reasonable (60–62), until more-robust evidence is available that higher daily doses of vitamin D are beneficial. Even this minimal amount of vitamin D (600 IU per day) is not received by many pregnant women worldwide (63, 64).

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SUPPLEMENTAL TABLE 1

Search strategies used for PubMed to identify randomized clinical trials to be included in a systematic review and meta-analysis to evaluate the effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes.

Preeclampsia
- #1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
- #2: "Pre-Eclampsia"[Mesh] OR "Preeclampsia" OR "Pre eclampsia" OR "Maternal Hypertension" OR "Hypertensive Disorders of Pregnancy"
- #3: #1 AND #2
- Filters: clinical trial, randomized clinical trial

Gestational diabetes
- #1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
- #2: "Diabetes, Gestational"[Mesh] OR "Gestational Diabetes" OR "Gestational Diabetes Mellitus" OR "Diabetes Pregnancy Induced"
- #3: #1 AND #2
- Filters: clinical trial, randomized clinical trial

VItamin D status at term
- #1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D" OR "Vitamin D Level" OR "Vitamin D Status" OR "25(OH) D levels"
- #2: "Pregnancy" OR "End of Pregnancy" OR "At Term Pregnancy"
- #3: #1 AND #2
- Filters: clinical trial, randomized clinical trial

Fetal growth retardation
- #1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
- #2: "Fetal Growth Retardation"[Mesh] OR "Intrauterine Growth Retardation" OR "Intrauterine Growth Restriction" OR "Fetal Growth Restriction"
- #3: #1 AND #2
- Filters: clinical trial, randomized clinical trial

Low and very low birth weight
- #1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
- #2: "Infant, Extremely Low Birth Weight"[Mesh] OR "Infant, Very Low Birth Weight"[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Infant, Small for Gestational Age"[Mesh] OR "Low Birth Weight"
- #3: #1 AND #2
- Filters: clinical trial, randomized clinical trial

Premature and very premature birth
- #1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
- #2: "Premature Birth"[Mesh] OR "Preterm Birth" OR "Premature Newborn" OR "Preterm Labor" OR "Very Premature Birth"
- #3: #1 AND #2
- Filters: clinical trial, randomized clinical trial

Birth weight
- #1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
- #2: "Birth weight" [Mesh] or "birth weight"
- #3: #1 AND #2
- Filters: clinical trial, randomized clinical trial

Cesarean section
- #1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
- #2: "Cesarean Section"[Mesh] OR "Cesarean Delivery" OR "Born by Cesarean"
- #3: #1 AND #2
- Filters: clinical trial, randomized clinical trial

Maternal mortality
- #1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
- #2: "Maternal Mortality"[Mesh] OR "Maternal Mortalities" OR "Maternal Deaths"
- #3: #1 AND #2
- Filters: clinical trial, randomized clinical trial

Birth length
- #1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
- #2: "Birth Length" OR "Size at Birth" OR "Stature at Birth"
- #3: #1 AND #2
- Filters: clinical trial, randomized clinical trial

Apgar score <7 at 5 min
- #1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
- #2: "Apgar Score"[Mesh] OR "Apgar test"

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Continued.

#3: #1 AND #2
Filters: clinical trial, randomized clinical trial
Still birth
#1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
#2: "Stillbirth"[Mesh]) OR "Fetal Death"[Mesh]
#3: #1 AND #2
Filters: clinical trial, randomized clinical trial
Neonatal infection
#1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
#2: "Neonatal Infection" OR "Neonatal Infectious Diseases"
#3: #1 AND #2
Filters: clinical trial, randomized clinical trial
Neonatal mortality
#1: "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Cholecalciferol"[Mesh] OR "Calcifediol"[Mesh] OR "Ergocalciferol" OR "Vitamin D Supplementation" OR "25-hydroxy-vitamin D"
#2: "Infant Mortality"[Mesh] OR "Neonatal Mortality" OR "Neonatal Mortalities"
#3: #1 AND #2
Filters: clinical trial, randomized clinical trial

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SUPPLEMENTAL TABLE 2

Comparison of recently published meta-analyses and our study of randomized clinical trials in a systematic review and meta-analysis to evaluate the effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes.

	Study, first author (reference # in text)			
Characteristic	**De Regil (9)**	**Thorne-Lyman (7)**	**Harvey (10)**	**Current study**
Year of publication	2012	2012	2014	2015
Type of review	Cochrane systematic review	Systematic review and meta-analysis	Systematic review	Systematic review and meta-analysis
Type of studies included	RCTs and quasi-randomized trials	RCTs and observational studies	RCTs and observational studies	RCTs
Primary objectives	To examine whether supplements with vitamin D alone or in combination with calcium or other vitamins and minerals given to women during pregnancy can safely improve maternal and neonatal outcomes	To assess the effect of vitamin D supplementation, intake or 25(OH)D status during pregnancy on perinatal and infant health outcomes	To investigate whether maternal supplementation with vitamin D in pregnancy leads to an improvement in maternal and neonatal outcomes	To evaluate the efficacy of vitamin D supplementation during pregnancy on obstetric and neonatal outcomes in RCTs
Type of participants	Pregnant women of any gestational or chronologic age, parity (no. of births), and no. of fetuses	Pregnant women	Pregnant women or pregnant women and their offspring	Pregnant women of any gestational or chronologic age and parity, without previous disease history
Type of intervention	Vitamin D supplementation during pregnancy irrespective of dose, duration, or time of commencement; trials testing vitamin D alone or in combination with other micronutrients as long as the intervention and the control group were treated similarly	Vitamin D from supplements or diet	Assessment of vitamin D status (dietary intake, sunlight exposure, circulating 25(OH)D concentration) or supplementation of participants with vitamin D or food containing vitamin D (e.g., oily fish)	Interventions of interest were: vitamin D alone vs. no treatment/placebo; vitamin D + calcium vs. no treatment/placebo; and vitamin D + calcium vs. calcium. Controls of interest were active controls, usual treatment without active control, and placebo.
Exclusion criteria	Crossover trials or any other observational studies	(1) nonhuman studies; (2) studies not in English, French, or Spanish; (3) reviews, case reports, and commentaries; (4) topics unrelated to the review; (5) studies that could not isolate the effects of vitamin D supplementation or intake; and (6) cross-sectional and nonprospective case–control studies	Studies were excluded if they were not written in English, were nonhuman studies, did not measure maternal vitamin D status in or immediately after pregnancy or supplement participants with vitamin D in pregnancy, or where an outcome of interest was not measured.	(1) no relevant control group; (2) data were not available or could not extracted for the study groups; and (3) studies that included a combination therapy of vitamin D + calcium + other vitamins and minerals
No. of studies included in quantitative synthesis	6	5 trials and 2 observational studies	19	13
Sample size in quantitative synthesis	32–502	126–228	NR	192–737
Quality assessment	GRADE assessment	Modified GRADE tool	Refined questionnaire based on Center for Reviews and Dissemination guidelines	Cochrane Collaboration Handbook risk-of-bias assessment tool
Methods of meta-analysis	As substantial statistical heterogeneity was detected, random-effects meta-analysis to produce an overall summary of an average	Inverse variance weights were used to generate pooled effect estimates with a fixed-effects model in absence of significant heterogeneity. In the	If no significant heterogeneity was noted, fixed-effect model analysis using the Mantel–Haenszel method; otherwise, results of the random-	Fixed-effects models and the Mantel-Haenszel method

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SUPPLEMENTAL TABLE 2

Continued.

Characteristic	Study, first author (reference # in text)			
	De Regil (9)	Thorne-Lyman (7)	Harvey (10)	Current study
	treatment effect across trials was used.	presence of significant heterogeneity, random-effects model was used.	effects model analysis using the DerSimonian–Laird method were used	
Primary outcomes	Maternal (preeclampsia, GDM, vitamin D status at term); infant (preterm birth, LBW)	LBW due to intrauterine growth restriction, preterm birth; neonatal growth/ morbidity/mortality; infant growth/ morbidity/mortality; maternal morbidity and mortality	Maternal osteomalacia, neonatal hypocalcemia, rickets, and reduced bone mass	Maternal (preeclampsia, gestational diabetes, change of vitamin D levels at term); neonatal (SGA, LBW, preterm birth, birth weight)
Secondary outcomes	Maternal (impaired glucose tolerance, cesarean section, gestational HTN, side effect, maternal death); infant (birth length and weight, head circumference, stillbirth, neonatal death, ICU admission, Apgar score, neonatal infection, very preterm birth)	NR	Maternal quality of life, neonatal body composition, and later offspring health outcomes (including asthma, diabetes mellitus, and immune disease)	Maternal (cesarean section and maternal mortality); neonatal (birth length, Apgar score, stillbirth, neonatal infection, very low weight (<1,500 g), very low preterm birth (<34 wk gestation), and neonatal mortality
Outcome association measure with 95% CI	Preeclampsia (RR 0.67, 95% CI 0.33–1.35); LBW (RR 0.48, 95% CI 0.23–1.01)	Protective effects of supplementation on LBW (RR 0.40, 95% CI 0.23–0.71) and nonsignificant but suggestive effects of daily supplementation on SGA (RR 0.67, 95% CI 0.40–1.11]); no effect on preterm delivery (<37 wk) was evident (RR 0.77, 95% CI 0.35–1.66)	Maternal 25(OH)D was associated with birth weight in meta-analysis of 3 observational studies using log-transformed 25(OH)D concentrations after adjustment for potential confounding factors (pooled regression coefficient 5.63 g/10% change maternal 25(OH)D, 95% CI 1.11–10.16 g)	Preeclampsia (RR 0.88, 95% CI 0.51–1.52); gestational diabetes (RR 1.05, 95% CI 0.60–1.84); SGA (RR 0.78, 95% CI 0.50–1.21); low birth weight (RR 0.72, 95% CI 0.44–1.16); and preterm birth (RR 1.26, 95% CI 0.60–2.63)
Conclusion	Vitamin D supplementation in a single or continued dose during pregnancy increases serum vitamin D concentrations as measured by 25-hydroxyvitamin D at term. The clinical significance of this finding and the potential use of this intervention as a part of routine antenatal care are yet to be determined, as the number of high-quality trials and outcomes reported is too limited to draw conclusions on its usefulness and safety.	Little evidence from trials exists to evaluate the effect of vitamin D supplementation during pregnancy on maternal, perinatal, or infant health outcomes. Based on both trials and observational studies, we recommend that future research explore SGA, preterm delivery, preeclampsia, and maternal and childhood infections, as outcomes of interest.	The evidence base is currently insufficient to support definite clinical recommendations regarding vitamin D supplementation in pregnancy. Although there is modest evidence to support a relationship between maternal 25(OH)D status and offspring birth weight, bone mass and serum calcium concentrations, these findings were limited by their observational nature (birth weight, bone mass) or risk of bias and low quality (calcium concentrations).	According to existing studies, vitamin D supplementation during pregnancy is not associated with better maternal and neonatal outcomes. Larger RCTs with better designs that evaluate clinically relevant outcomes are necessary to reach a definitive conclusion.

Note: CI = confidence interval; GDM = gestational diabetes mellitus; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; HTN = hypertension; ICU = intensive care unit; LBW = low birth weight; NR = not reported; RCT = randomized controlled trial; RR = relative risk; SGA = small for gestational age; 25(OH)D = 25-hydroxyvitamin D_3.

Pérez-López. Vitamin D supplementation and pregnancy. Fertil Steril 2015.