Vitamin D supplementation during pregnancy to prevent vitamin D deficiency in newborns: a systematic review and meta-analysis

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Abstract

Objectives: to assess the effects of vitamin D supplementation during pregnancy on the outcomes of vitamin D concentration in newborns, length at birth, overall health (Apgar), birth weight and maternal vitamin D concentration after childbirth.

Methods: this research was conducted in the electronic databases of MEDLINE, LILACS, EMBASE and Cochrane Library until December 2020, using the terms "vitamin D", "pregnancy", "vitamin D deficiency", "infant", "newborn" and their synonyms. Randomized controlled trials were searched by evaluating the effects of maternal vitamin D supplementation in neonates. The data was analyzed on RevMan 5.4 software and the quality of evidence on GRADE.

Results: the newborn's overall health condition was presented as Apgar, with a mean difference (MD) of 0.15 (CI95%=0.06-0.25; p=0.002; I^2=0%, two studies, 648 participants, moderate quality evidence) at the first minute and 0.11 (CI95%=0.04-0.17; p=0.001; I^2=0%, two studies, 648 participants, moderate quality evidence) at the fifth minute. Significant effects were also presented at the length at birth considering any supplemented dose (MD=0.19; CI95%=0.08-0.30; p=0.0010; I^2=0%, 1452 participants, low quality evidence) and birth weight in doses higher than 4000IU/day (MD=257.05 (CI95%=137.81-376.29; p<0.0001; I^2=14%, 176 participants, moderate quality evidence).

Conclusion: vitamin D supplementation during pregnancy improves serum 25 (OH) D concentration and suggests positive effects on overall health condition, length at birth and birth weight. PROSPERO CRD42017073292.

Key words *Vitamin D, Dietary supplements, Pregnancy, Child, Infant, Newborn*

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Introduction

Vitamin D differs from other vitamins because of its pre-hormone functions, although it is defined as a vitamin. Vitamin D can be obtained from several dietary sources, such as cod liver oil and fatty fish (wild salmon, sardines and mackerel).[1] However, endogenous cutaneous synthesis represents the most important source of this vitamin.[1] The recommended daily intake of vitamin D for a healthy population is 600IU until the age of 70 - no difference for pregnant women. For individuals over 70 years of age, the recommendation is 800IU of vitamin D daily.[2] Serum vitamin D levels between 30 and 100ng/mL (75 and 250nmol/L) are recommended, and levels between 20 and 29ng/mL (50-74nmol/L) are considered insufficient and below 20ng/mL (50nmol/L) are called deficient.[1]

Currently, an increase in vitamin D deficiency in the general population is indicated.[3] Among the risk factors attributed to vitamin D deficiency, the most prevalent are: lack of sun exposure, skin pigmentation, low intake of meat, fish and eggs, extreme age, obesity and use of medications, including anticonvulsants, antiretrovirals and corticosteroids.[3]

Vitamin D deficiency in women of childbearing age is increasing due to daily lifestyle, including increased time spent in work environments, closed home environments, maternal obesity, and overuse of broad-spectrum sunscreens.[4]

Vitamin D is essential for the pregnant woman and the child's health. Concentrations of 25-hydroxyvitamin D in the fetal and neonatal circulation depend on maternal vitamin D concentrations.[5] During gestation, vitamin D deficiency or insufficiency may be related to insufficient weight gain, preeclampsia (PE), gestational diabetes (GDM), premature birth and disorders in the child's bone homeostasis.[6,7]

At childhood, low levels of 25-hydroxyvitamin D are related to asthma, atopy, obesity, inflammatory diseases and a higher incidence of pneumonia, recurrent urinary tract infection and sepsis.[8] A previous study has shown that children affected by these diseases have a higher frequency of vitamin D deficiency or insufficiency when compared to children in the control group.[9] Föcker *et al*.[10] suggest a relation between mental health in childhood and adolescence with vitamin D deficiency.

Worldwide, 54% of pregnant women and 75% of live births have vitamin D concentrations less than 50nmol/L, which is a threshold commonly used to describe the deficiency of the vitamin in question.[11] Thus, this systematic review aimed to analyze the effect of vitamin D supplementation during gestation for the prevention of vitamin D deficiency in newborns and its effects on weight, length at birth and cephalic perimeter at birth, overall health condition (Apgar of neonates) and maternal vitamin D concentration after childbirth.

Methods

This present study is a systematic review following the PRISMA guidelines.[12] The review protocol was registered at PROSPERO (Prospective International Registry of Systematic Reviews, http://www.crd.york.ac.uk/prospero; CRD42017073292).

We searched the following electronic databases from inception up to December 2020: MEDLINE, LILACS, EMBASE and Cochrane Library, using free and indexed terms: "vitamin D", "pregnancy", "vitamin D deficiency", "25-hydroxyvitamin D", "infant", "newborn", "child", "vitamin D supplementation", "clinical trials" and their synonyms to search relevant studies. The research was limited to humans, regardless of the language of the studies analyzed. The lists of references of all the selected studies were checked as well as the grey literature. In addition, references to relevant meta-analysis, guidelines and comments identified in the Medline, LILACS and Cochrane Library were checked.

The inclusion of articles for this review followed the PICO:

P (*Participants*): Pregnant women who received vitamin D supplementation
I (*Intervention*): Vitamin D supplementation
C (*Comparison*): Placebo
O (*Outcomes*): Primary: vitamin D concentration in the newborn
Secondary: length at birth, overall health (Apgar), birth weight and maternal vitamin D concentration after childbirth
S (*Study type*): Randomized controlled trials

After running the search strategies in the databases, the selected titles were exported to Endnote to identify the duplicate studies and then sent to Covidence for titles and abstracts reading. Two reviewers (A.S.P and J.P.S) independently analyzed the titles and abstracts of the studies acquired by the search strategies. Potential articles for inclusion were selected for full-text reading. Disagreements were solved with the help of a third reviewer (T.C).

Two researchers (A.S.P and J.P.S) independently extracted the data from the primary studies. A standardized form was used with the following information: author, year, country, study objectives, patient characteristics, methods, intervention information and results of each included study.

All the included studies were evaluated for their methodological quality. The Cochrane Collaboration risk of bias tool used the RevMan 5.4 software. Criteria for risk of bias consisted of 7 items: random sequence generation, allocation concealment, blinding of participants and

researchers, blinding of outcome assessment, incomplete results data, selective outcome reports, and other sources of bias. For the quality assessment of the evidence produced in this systematic review, we used the GRADE online.

According to the *Cochrane Handbook for Systematic Reviews of Interventions*, it is recommended that meta-analyzes includes at least 9 studies to perform asymmetry analysis of the funnel graph. Thus, it was not recommended to test the asymmetry of the funnel graph because of the low number of studies included per assessed outcome.

Data were analyzed using RevMan 5.4 software. Mean and standard deviation with 95% confidence interval were used. Pooled effect estimates used the Mantel-Haenszel random effect method. Study heterogeneity was determined using I^2 (where values greater than 75% suggest substantial heterogeneity)[13] and *p*-values of test χ^2. Results were expressed through tables and graphics.

Results

The search identified a total of 484 studies. Of these, 68 studies were duplicates. The remaining 416 articles were exported to Covidence, online software that assists in performing systematic reviews, for reading titles and abstracts. Of these, 334 articles were excluded after reading titles and abstracts and 82 studies were analyzed in full text. After completing the reading, 65 articles were excluded because they did not meet the criteria; 25 presented a different intervention, nine had a different population analysis, eight had no design of the study proposed, seven were protocols, seven had no corresponding outcomes, three studies were not found (the authors of the studies were contacted, had no replies), two analyzed the adult population, two were not a RCTs (different design), one had a different comparator and one had the indication of incorrect intervention. Thus, 17 articles were included in the qualitative analysis of this systematic review. The process of selecting studies is summarized in Figure 1. Seventeen primary studies involving 3491 patients met the inclusion criteria and were analyzed. The characteristics of all included studies are summarized in Table 1. The studies were published between the years 1980 to 2018. All studies included pregnant women who were supplemented with vitamin D during pregnancy.

Bias Risk

Cochrane risk of bias tool was used to assess risk of bias of the included studies. The articles were classified as low risk, high risk or unclear risk of bias according to each criterion met.

Five studies were judged as low risk of bias for all items analyzed.[14-18] Two studies were unclear regarding randomization and allocation concealment.[19,20] Five studies were unclear how the allocation concealment was done.[21-26] One study was unclear in the analysis with incomplete results.[22] Four studies did not blind the participants/researchers and neither the people who measured the outcomes. Kalra *et al*.[27] was unclear in allocation concealment, participant/researcher and the result assessor's blinding. Rodda *et al*.[28] was unclear in allocation concealment and the result assessor's blinding and were at high risk of bias for participant/investigator's blinding. Sablock *et al*.[29] was unclear for blinding the participants/researchers. Yesiltepe-Mutlu *et al*.[30] was unclear in the randomization and allocation concealment, high risk of bias for participant/investigator and the result assessor's blinding (Figure 2).

Serum vitamin D concentration at birth

All seventeen studies evaluated vitamin D concentration in newborns of supplemented mothers and placebo mothers, and the results were analyzed using a random effects metanalysis. Only doses higher than 4000 to 6000IU/day demonstrated a positive effect on vitamin D concentration in newborns of supplemented mothers when compared with the placebo mothers at the time of childbirth. However, supplements below 500IU/day to 4000IU/day did not show a significant effect on neonatal serum vitamin D compared to placebo. Doses between 4000IU/day and 6000IU/day showed a significant effect (p=0.04), but had high heterogeneity in the included studies (I^2=98%)

Length at birth

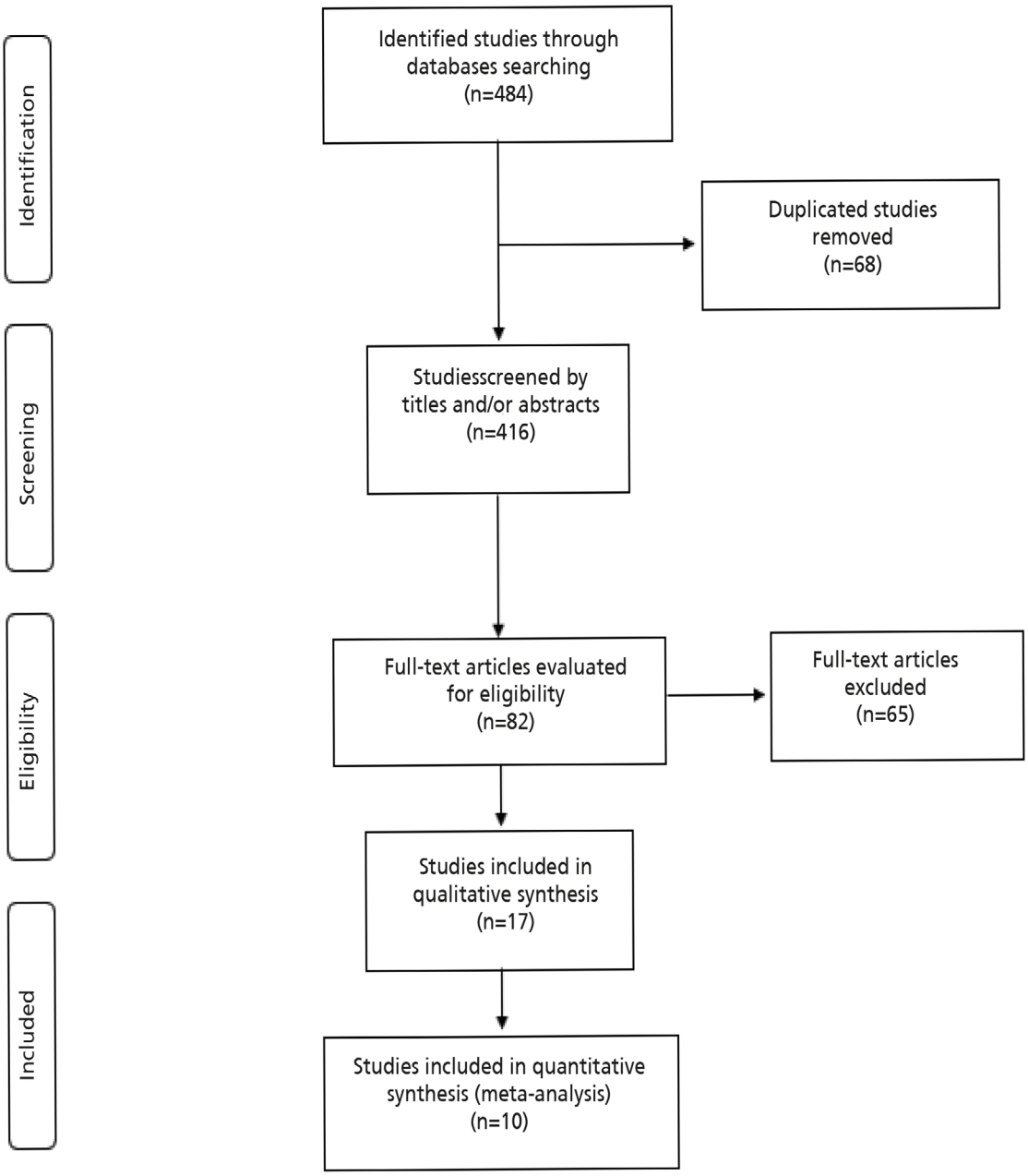
A total of seven articles analyzed the height (cm) of the neonates and compared them to the group supplemented with placebo. Supplementation doses varied from 200IU/day[22] to a maximum of 120,000IU divided into one dose in the second trimester and one dose in the third.[27] The results were analyzed using the fixed effect. The difference in mean height was 0.19 (95%CI=0.08 - 0.30; p=0.0010; I^2=0%, 1452 participants, low quality evidence). We downgraded the quality of evidence (-2) due to very serious risk of bias. Thus, maternal supplementation of vitamin D during gestation seems to bring benefits in relation to length at birth (Figure 3A).

Overall health status

Two studies[24,25] analyzed the results for overall health status (Apgar test) comparing group receiving vitamin D supplementation and placebo. The supplementation dose was 4000IU/day or 50,000IU every 2 weeks, respectively. The results were analyzed using the fixed effect, with a mean difference of 0.15 (CI95%=0.06-0.25; p=0.002; I^2=0%, two studies, 648 participants, moderate quality

Figure 1

Flowchart of the different phases of the systematic review.



evidence) for the 1 min. test and 0.11 (CI95%=0.04-0.17; p=0.001; I^2=0%, two studies, 648 participants, moderate quality evidence) for the 5 mins. test. We downgraded the quality of evidence (-1) due to the risk of bias. Thus, children whose mothers were supplemented with vitamin D showed better performance in the test (Figure 3B).

Birth weight

In relation to birth weight (g), after the analyses, it could be concluded that maternal doses of up to 4000IU/day of vitamin D supplementation, the parameters remained unaltered . However, the two studies that evaluated doses higher than 4000IU presented favorable results for the supplementation group MD=257.05 (CI95%=137.81-376.29; p=<0.0001; I^2=14%, 176 participants, moderate quality evidence) (Figure 4). We downgraded the quality of evidence (-1) due toserious risk of bias.

Maternal vitamin D serum concentration

The maternal vitamin D serum concentration was analyzed by fifteen studies at different dosages. All the results were analyzed using the random analysis method. Doses ranged from 500 to 6000IU/day. Although all doses above 1000IU/day analyzed presented results with statistical significance

Table 1

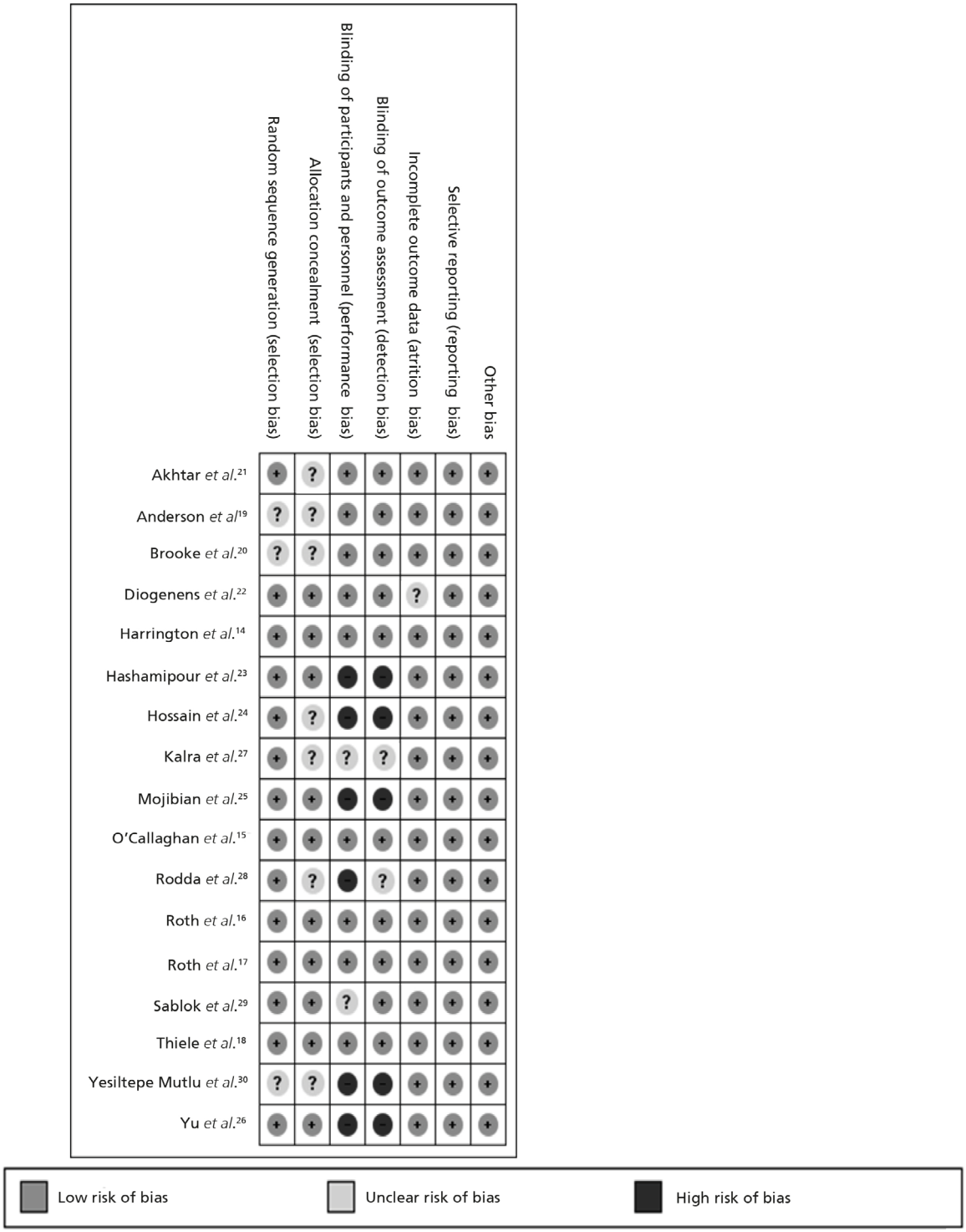
Characteristics of the included studies.

Author/Year	Country	Type of Study	Mean age	Total number of participants	Number of participants supplemented group	Type of supplementation and dose	Comparison	Time	Outcomes evaluated by the authors
Akhtar *et al.*,[21] 2016	Bangladesh	RCT	Vitamin D group:22.43 ± 3.75; Placebo group: 22.85 ± 1.47	80	40	Vitamin D3 Pill 3500IU/week	Placebo oil (Miglyol oil, Merck)	26-29 weeks of gestation until childbirth	1) Serum concentration of vitamin D at umbilical cord 2) Effect of prenatal supplementation at T and B cells of the umbilical cord function 3) Cytokine concentrations in stimulated umbilical cord blood lymphocytes
Anderson *et al.*,[19] 2018	USA	RCT	Not informed by the authors	13	7	Vitamin D3 pill 400IU + 3.400IU/ day	Prenatal vitamins containing 400IU vitamin D3 + placebo pill /day	24-28 weeks until 4-6 weeks after	1) maternal serum concentration of vitamin D at at birth and 4-6 weeks after 2) Neonatal serum concentration of vitamin D of at 4-6 weeks after 3) Effect of prenatal supplementation at maternal DNA methylation and breastfeeding
Brooke *et al.*,[20]1980	England	ECR	Vitamin D group: 23.9±4-8; Control group: 23.7±3-1	126	59	Calciferol (D2) 1000i U/day	Placebo not specified by the author	28-32 weeks until term	1) Serum concentration of maternal vitamin D, calcium, phosphate, albumin, phosphatase alkaline, andvitamin D carrier globulin at term 2) Serum concentration in the umbilical cord of vitamin D, calcium, phosphate, albumin, alkaline phosphatase, placental and vit D carrier globulin 3) Anthropometric of the newborns
Roth,[16] 2013	Bangladesh	RCT	22.2 (±3.1)	160	80	Liquid formulation of Vitamin D3 Group 1: Single dose of 70,000IU at day 0 followed by 35000IU/week starting on day 7 until childbirth Group 2: 14,000IU/week starting at day 0 until childbirth	Non-pregnant women that received a single dose of 70,000IU at day 0 followed by 35000IU/week starting on day 7 (10 weeks of supplementation)	27-30 weeks until childbirth	1) Maternal serum concentration of vitamin D, calcium, PTH, adjusted calcium-albumin, and urinary calcium-creatinine ratio at childbirth 2) Serum vitamin D concentration in the umbilical cord
Sablok *et al.*,[29] 2015	Índia	RCT	Not informed by the authors	165	108	Cholecalciferol 1) Sufficient>50nmol/L: (1 dose) 60000IU with 20 weeks 2)Insufficient25-50nmol/L: (2 doses) 120000IU with 20 and 24 weeks 3)Deficient<25nmol/L: (4 doses) 120000IU with 20, 24, 28, 32 weeks	Placebo not specified by author	14-20 weeks until 32 weeks of gestation	1) Maternal serum vitamin D concentration 2) Serum concentration of vitamin D in the umbilical cord 3) Birth weight and Apgar 4) Gestational complications
Thiele *et al.*,[18] 2017	USA	RCT	Vitamin D group: 30 ± 6.0 Control: 27 ± 5.5	13	7	Pill of Vitamin D3 400IU vitamin D3 + 3400IU of vitamin D in pill /day	Prenatal vitamin containing 400IU vitamin D3 plus a placebo pill, both taken daily	24-28 weeks until 4-6 weeks after childbirth	1) Concentration of vitamin D, calcium and maternal PTH at birth and 4-6 weeks after 2) Concentration of neonatal vitamin D 24-72 hours after birth and 4-6 weeks after 3) Anthropometric measurements of the newborn

Yesiltepe-Mutlu *et al.*,[30] 2014	Turkey	RCT	Vitamin D Group 1: 26.2 ± 4.5 Vitamin D Group 2: 26.6 ± 4.8 Control Group: 29 ± 5.7	91	63	Cholecalciferol in drops (50000IU in 15ml) Group 1: n=31 -> 1200IU/day Group 2: n=32 -> 2000IU/day	600IUI/day of Cholecalciferol	Starting at 13-32 weeks until 3 months after the initiation of vitamin D supplementation	1) Maternal serum concentration of vitamin D, calcium, PTH, phosphorus and alkaline phosphatase 2) Neonatal serum concentration of vitamin D, calcium, PTH, phosphorus and alkaline phosphatase 3) Birth weight
Yu *et al.*,[26] 2009	England	RCT	Asians: Mean of 29 years Middle East: Mean of 31 years Black: Mean of 31 years Caucasians: Mean of 33 years	179	120	Calciferol Group 1: n=60 -> 800IU/day ergocalciferol Group 2: n=60 -> 200000IU/single dose calciferol	No supplementation	27 weeks until childbirth	1) Serum concentration of vitamin D, corrected calcium, maternal PTH at childbirth 2) Serum concentration of vitamin D and corrected calcium in the umbilical cord
O'Callaghan *et al.*,[15] 2018	Ireland	RCT	Vitamin D Group 1: 34 ± 4 Vitamin D Group 2: 35 ± 3 Placebo group: 32 ± 4	144	Group 1 and 2 Final: 48/48	Vitamin D3 pill Group 1: 400IU/day Group 2: 800IU/day	Placebo with <0.02 µg/day of Vitamin D3	Starting at<18 weeks (mean of 14) until 34-38 weeks (mean of 36)	1) Maternal serum concentration of 25 (OH) D, PTH and Ca before and after supplementation 2) Dosage of 25 (OH) D in the umbilical cord
Roth *et al.*,[17] 2018	India	RCT	23 years	1300	Group 1: 260 (4.200IU/week) Group 2: 259 (16.800IU/week) Group 3: 260 (28.000IU/week) Group 4: 260 (28.000IU/week + 26 week after childbirth)	Vitamin D3 pill Group 1: 4.200IU/week Group 2: 16.800IU/week Group 3 : 28.000IU/week Group 4: 28.000IU/week until 26 weeks after childbirth	Placebo not specified by the author	Starting between 17-24 weeks until childbirth (group 1,2 3, 4) or until 26 weeks after postpartum (group)	1) Maternal concentration of 25 (OH) D and PTH 2) Anthropometric data of the NB and growth monitoring up to 1 year of age
Rodda *et al.*,[28] 2015	Australia	RCT	Vitamin D group: 28.3 Control group: 29.2	45	22	Vitamin D3 pill 2000IU/day -> 4000IU/day for those who were still deficient at 28 weeks	No supplementation	Starting between 12-16 weeks until 28 weeks. Women who were still deficient at 28 weeks had the dose doubled to 4000IU/day	1) Maternal serum concentration before and after supplementation 2) Dosing of 25 (OH) D in the umbilical cord
Mojibian *et al.*,[25] 2015	Iran	RCT	Vitamin D group: 27.8 ± 5 Control group: 27.3 ± 4.9	470	224	Cholecalciferol pill 50000IU each 2 weeks	400IU/day of Cholecalciferol	Starting at 12 weeks until delivery	1) Maternal 25 (OH) D concentration + maternal TTGO 2) Concentration of umbilical cord 25 (OH) D 3) Anthropometric data of NB and Apgar

Hossain *et al.*,[24] 2014	Pakistan	RCT	Vitamin D group: 25.96 ± 3.13 Control group: 25.19 ± 4.36	175	86	Vitamin D3 capsule + routine antenatal care 4000IU/day + 400mg/ dayof ferrous sulfate and 600mg/day of calcium lactate	Routine antenatal care	Starting at 20 weeks until childbirth	1) Maternal concentration of 25 (OH) D 2) Complications during pregnancy 3) Concentration of 25 (OH) D in the neonate 4) Anthropometric data of the NB and Apgar
Kalra *et al.*,[27] 2012	Índia	RCT	Vitamin Group 1: 26.3 ± 4.2 Vitamin Group 2: 27.0 ± 3.8 Usual care (Group 3): 26.2 ± 3.7	139	Group 1: 48 Group 2: 49 Group 3: 43	Cholecalciferol oil pill Group 1: 60.000IU, single dose at 2nd trimester Group 2: 120.000IU double dose, at 2nd trimester and another at 3rd trimester and 1 g/day of Ca	Usual care (no vitamin D supplementation)	Group 1: single dose at 2nd trimester Group 2: double dose, one at 2nd and another at 3rd trimester	1) Concentration of 25 (OH) D, PTH and maternal Ca 2) Complications during pregnancy 3) Concentration of 25 (OH) and Ca in the umbilical cord 4) Anthropometric data of the NB
Diogenes *et al.*,[22] 2015	Brazil	RCT	Intervention group: 16.8 ± 1.5 Placebo group: 17.2 ± 1.0	56	30	Cholecalciferol + Calcium 200IU/day + 600mg/day	Placebo not specified by the authors	Start ing between 21-29 weeks until childbirth	1) Concentration of 25 (OH) D and maternal Ca 2) Concentration of 25 (OH) D in the umbilical cord 3) Anthropometric data 4) Growth assessment during pregnancy (femur size)
Harrington *et al.*,[14] 2014	Bangladesh	RCT	Not informed by the authors	130	67	Cholecalciferol 35.000IU/week (5.000IU/ day)	Adminstrated Oil-based no vitamin D3	Starting between 26 and 30 weeks until childbirth	1) Maternal concentration of 25 (OH) D, Ca, albumin, PTH 2) Concentration 25 (OH) D, Ca, albumin, and PTH in umbilical cord
Hashemipour *et al.*,[23] 2013	Iran	RCT	Vitamin D group: 25.05 ± 4.62 Control group: 27.62 ± 4.63	109	54	Cholecalciferol 50.000IU/week for 8 weeks (starting between 26-28 weeks)	Multivitamin containing 400IU vitamin D3 plus 200mg/day of Ca until the end of pregnancy	Starting supplementation of 50.000 between 26-28 weeks during 8 weeks	1) Concentration of 25 (OH) D and maternal Ca 2) Concentration of 25 (OH) D in the umbilical cord and serum Ca of the NB

Figure 2
Summary of bias risk.



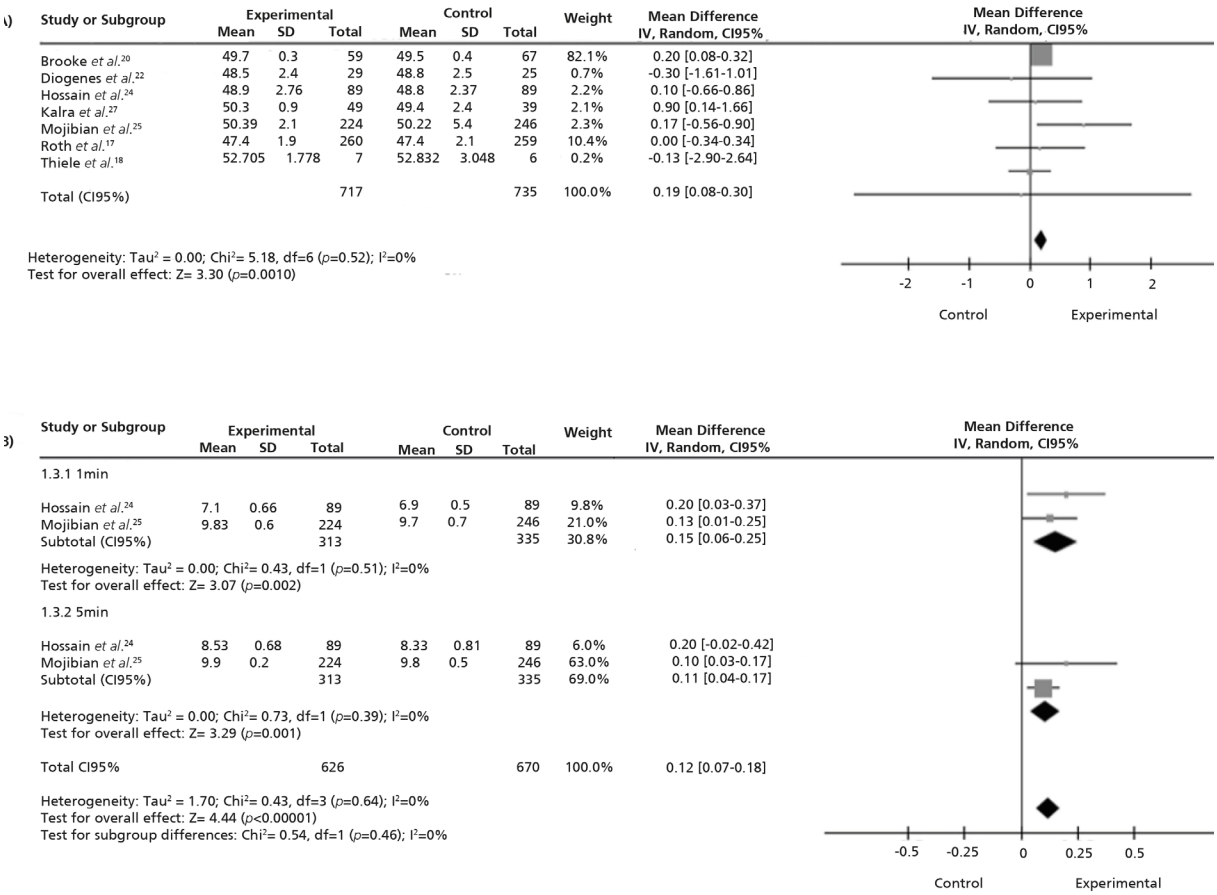
for mothers who received the supplementation compared to the control (p<0,002), but due to the high heterogeneity of the studies (I^2>90), we can only infer that a dose up to 500IU/day does not have any benefit to increase maternal concentrations. Of these, two studies[15,22] used doses lower than 500IU/day, with a mean of -0,16 (CI95%=-0.56-0.24; p=0.43; I^2=27%, 139 participants; high quality evidence).

Discussion

This review aimed to synthesize the evidence on vitamin D supplementation during pregnancy and its effects on maternal serum concentration, neonatal serum concentration, neonatal anthropometric indices, and overall health status (Apgar). Saraf *et al.*,[11] stated that

Figure 3

Forest graph: Vitamin D x placebo.



3A = Forest graph: Vitamin D x placebo for length at birth; 3B = Forest graph: Vitamin D x placebo for overall health status.

vitamin deficiency during pregnancy is very common and since the fetus and newborn are dependent on maternal vitamin D values,[31] supplementation is recommended for pregnant women.[32]

Windham *et al.*,[33] in their study, consider vitamin D levels below 50nmol/L as deficient, between 50 and 74nmol/L as insufficient, and greater than 75nmol/L sufficient. Within these parameters, this review showed that doses greater than 6000IU/day of maternal supplementation are necessary to achieve serum concentrations considered sufficient in the neonate.[26,27,29]

In addition, in our review, vitamin D supplementation during pregnancy has been shown to have a positive effect on neonatal length and Apgar at 1st and 5th minutes of life. However, no difference of effect was seen in the head circumference at birth of the supplementing group as compared to placebo.

Corroborating these results, Sabour *et al.*,[34] evaluated maternal and neonatal vitamin D concentration of 449 women and their newborns and correlated sufficient vitamin D levels with a more satisfactory 1st minute Apgar score. Studies by Yap *et al.*,[35] and Maghbolli *et al.*,[36] showed that there was no relationship between the concentration of vitamin D and the increase in Apgar in the 1st and 5th minute of life.

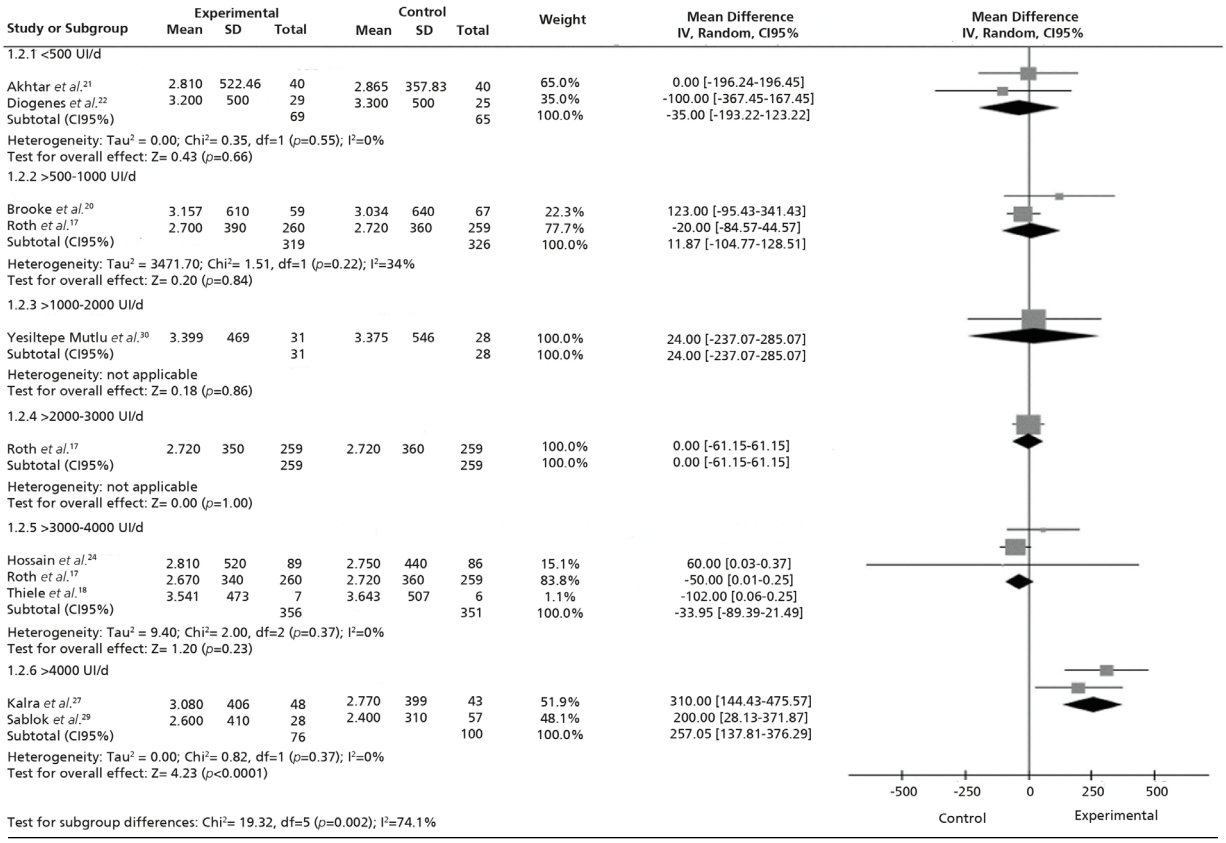
As in the results of our study, Hashemipour *et al.*,[37] demonstrated that children of supplemented mothers were taller (0.8 cm taller) and had a larger head circumference compared to the control group (50,000IU/week per 8 weeks + 400IU/day associated with calcium throughout pregnancy). Marya *et al.*,[38] also found significant differences in the length at birth and head circumference of newborns of mothers supplemented with two doses of 15,000 mcg of vitamin D in the third trimester.

Asemi *et al.*,[39] analyzed the effects of 50,000IU vitamin D supplementation in pregnant women through a randomized controlled trial, where they found no significant effect on vitamin D supplementation in relation to birth weight, contributing to the findings of the present study. In another study, Blighe *et al.*,[40] also show the unrelation of prenatal vitamin D supplementation with positive effects on newborn's weight.

Two other studies showed that there was no relation between vitamin D concentration and length and head circumference at birth.[35,36] Asemi *et al.*,[41] did not relate increased length and head circumference with vitamin

Figure 4

Forest graph: Vitamin D x placebo for birth weight.



D supplementation of 200IU/day. Brough *et al.*,[42] had a low relation with micronutrient supplementation, including vitamin D (200IU/day), head circumference and length at birth. Charandabi *et al.*,[43] did not observe significant differences in length and head circumference at birth following calcium + vitamin D supplementation (1000IU/day) for 8 to 9 weeks in the third trimester.

Regarding the ideal gestational age for the beginning of supplementation, it was not possible to evaluate in this systematic review, due to the low quality of some studies and their heterogeneity. More randomized controlled trials assessing the most effective gestational age to start vitamin D supplementation are needed to prevent vitamin D deficiency in children under the age of five.

The present study had some limitations regarding the analysis of time and dosage of vitamin D supplementation, as well as the gestational age for the therapeutic approach. The included studies did not use a standard dosage for supplementation, which influenced the confidence intervals (imprecision) presented in the review. Future studies are needed to assess the therapeutic potential of vitamin D supplementation in pregnant women for the prevention of vitamin D deficiency in newborns.

Implications for practice: The present systematic review evaluated the effects of maternal vitamin D supplementation on maternal and neonatal serum 25(OH)D concentration, overall health status (Apgar score), length at birth and birth weight. Vitamin D supplementation during pregnancy was effective in changing the parameters of lengthat birth, overall health status (Apgar), as well as neonatal vitamin D concentration at doses above 6000IU. Maternal vitamin D serum concentration had a significant effect when supplemented with doses above 1000IU/day. On the other hand, the studies evaluated regarding birth weight and head circumference showed no significant effect compared to placebo.

Implications for future research: Based on the results of this review, new clinical trials can be carried out seeking to determine a standard dose that is more effective for the population studied here, indicating the dose for treatment according to gestational age and duration of use of the supplementation, for example, during the entire period of pregnancy or at some specific trimester, to achieve the best effects.

Authors' contribution

Colonetti T and Rosa MI: conceptualization, formal analysis, methodology, project administration, validation, writing – original draft, writing – review & editing. Paulino AS and Sartor JP: data curation, formal analysis,

investigation, writing – original draft. Grande AJ: formal analysis, methodology, writing – original draft. Colonetti L: investigation, writing – original draft, writing – review & editing. All authors approved the final version of the article and declare no conflict of interest.

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