Clinical Nutrition 39 (2020) 1742-1752



Contents lists available at ScienceDirect

Clinical Nutrition



journal homepage: http://www.elsevier.com/locate/clnu

Meta-analyses

Vitamin D supplementation and incident preeclampsia: A systematic review and meta-analysis of randomized clinical trials



Silvia Fogacci ^a, Federica Fogacci ^a, Maciej Banach ^{b, c, d, *}, Erin D. Michos ^{e, f}, Adrian V. Hernandez ^{g, h}, Gregory Y.H. Lip ⁱ, Michael J. Blaha ^e, Peter P. Toth ^{e, j}, Claudio Borghi ^a, Arrigo F.G. Cicero ^{a, **}, on behalf of the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group

^a Department of Medicine and Surgery Sciences, University of Bologna, Bologna, Italy

^b Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Poland

^c Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland

^d Cardiovascular Research Centre, University of Zielona Gora, Zielona Gora, Poland

^e The Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins School of Medicine, Baltimore, MD, USA

^f Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

^g Health Outcomes, Policy, and Evidence Synthesis (HOPES) Group, School of Pharmacy, University of Connecticut, Storrs, CT, USA

^h Vicerrectorado de Investigacion, Universidad San Ignacio de Loyola (USIL), Lima, Peru

ⁱ Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK

^j Preventive Cardiology, CGH Medical Center, Sterling, IL, USA

A R T I C L E I N F O

Article history: Received 5 August 2019 Accepted 17 August 2019

Keywords: Vitamin D Pregnancy Preeclampsia Meta-analysis

SUMMARY

Background: Maternal vitamin D deficiency has been associated with an increased risk for preeclampsia. Despite this, the current evidence regarding the efficacy of vitamin D supplementation in preventing preeclampsia is controversial. To assess the impact of vitamin D supplementation on the risk of preeclampsia, we performed a systematic review of the literature and a meta-analysis of the available randomized clinical trials (RCTs).

Methods: The primary outcome was preeclampsia. Subgroup analyses were carried out considering the timing of the supplementation, type of intervention and the study design. Meta-regression analysis, including the amount of vitamin D and maternal age, were planned to explore heterogeneity (PROSPERO database registration number: CRD42019119207).

Results: Data were pooled from 27 RCTs comprising 59 arms, which included overall 4777 participants, of whom 2487 were in the vitamin D-treated arm and 2290 in the control arm. Vitamin D administration in pregnancy was associated with a reduced risk of preeclampsia (odd ratio [OR] 0.37, 95% confidence interval [CI]: 0.26, 0.52; $I^2 = 0$ %). If the vitamin D supplementation was started up to 20 weeks' gestation, the odds was a little lower (OR 0.35, 95% CI: 0.24, 0.50, p < 0.001). The effect was largely independent of the supplementation cessation (until delivery or not), type of intervention (vitamin D alone or in association with calcium), and study design. Increasing dose of vitamin D was associated with reduced incidence of preeclampsia (slope of log OR: -1.1, 95% CI: -1.73, -0.46; p < 0.001).

Conclusions: Results suggest that vitamin D supplementation may be useful in preventing preeclampsia. These data are especially useful for health-care providers who engage in the management of pregnant women at risk for preeclampsia. Our findings are a call for action to definitively address vitamin D supplementation as a possible intervention strategy in preventing preeclampsia in pregnancy.

© 2019 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.clnu.2019.08.015

0261-5614/© 2019 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

^{*} Corresponding author. Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113, 90-549 Lodz, Poland. Fax: +48 42 639 37 71.

^{**} Corresponding author. Medical and Surgical Sciences Department, Sant'Orsola-Malpighi University Hospital, Via Albertoni, 15, 40138 Bologna, Italy. Fax: +39 51391320. E-mail addresses: maciejbanach77@gmail.com (M. Banach), arrigo.cicero@unibo.it (A.F.G. Cicero).

1. Introduction

Vitamin D deficiency, as measured by circulating 25(OH)vitamin D concentrations, is reported to be as high as 40% among pregnant women and is also very common and profound during lactation [1]. In Mediterranean countries, where vitamin D deficiency is even more prevalent (up to 60–80%), neither vitamin D supplementation nor policies of food fortification are currently recommended during pregnancy, and they remain entirely absent from clinical practise [2]. As pregnancy progresses, the requirements of vitamin D increase and consequently, any preexisting vitamin D deficiency can worsen [3]. In particular, a compromised maternal vitamin D status has been associated with an approximately two-fold increased prevalence of congenital heart defects in offsprings and a higher incidence of fetal miscarriage, gestational diabetes, bacterial vaginosis and perinatal depression in mothers, other than impaired fetal and childhood growth [3–5]. Furthermore, inadequate plasma 25(OH)-vitamin D concentration during early pregnancy seems to be associated with more pronounced changes in total cholesterol and low-density lipoprotein cholesterol throughout gestation [6], and with an increased risk of developing hypertensive disorders [7].

In a cohort study performed on 13 806 pregnant women, maternal vitamin D deficiency at 23–28 weeks of gestation was strongly associated with an increased risk for severe preeclampsia after adjustment for relevant confounders (odd ratio [OR] 3.16, 95% confidence interval [CI]: 1.77–5.65) [8]. To date, vitamin D supplementation has been demonstrated to potentiate nifedipine treatment for preeclampsia, shortening the time to control blood pressure and prolonging time before subsequent hypertensive crisis, probably *via* an immunomodulatory mechanism [9], though data on the effect of vitamin D supplementation in preventing the onset of preeclampsia in pregnancy are still inconclusive [10].

For this reason, we aimed to assess the impact of vitamin D supplementation on the risk of preeclampsia through a systematic review of the literature and a meta-analysis of the available randomized controlled clinical trials [RCTs].

2. Methods

The study was designed according to guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [11], and was registered in the PROSPERO database (ID: CRD42019119207). Due to the study design (meta-analysis), neither Institutional Review Board (IRB) approval, nor patient informed consents were required.

2.1. Search strategy

PubMed, SCOPUS, Google Scholar and ISI Web of Science by Clarivate databases were searched, with no language restriction, using the following search terms: ("Vitamin D" OR "Hydrox-"25(OH)D" (25(OH)D)" vvitamin D OR OR "25hydroxycholecalciferol") AND ("Pregnancy" OR "Pregnant women" OR "Gestation") AND ("Clinical trial" OR "Clinical study" OR "study" OR "prospective study" OR "Randomized controlled trial" OR "RCT"). The wild-card term "*" was used to increase the sensitivity of the search strategy, which was limited to studies in humans. The reference list of identified papers was manually checked for additional relevant articles. In particular, additional searches for potential trials included the references of review articles on that issue, and the abstracts from selected congresses on the subject of the meta-analysis. Literature was searched from inception to January 21st, 2019.

2.2. Study selection criteria

Original studies were included if they met the following criteria: (i) being a prospective randomized controlled trial with either multicentre or single-centre design, (ii) having at least a single dose of vitamin D prescribed in the active group, (iii) having a control group for vitamin D supplementation, (iv) involving pregnant women not treated with vitamin D before gestation, (v) testing the safety of vitamin D administration, (vi) reporting all the adverse events occurred during the treatment.

Studies were also excluded according to the following criteria: (i) lacking an appropriate controlled design for vitamin D supplementation or testing multivitamin or multimineral supplements with vitamin D; (ii) studies with the overlapping participants with other studies; (iii) reviews, letters or comments; (iv) populationbased cohort studies. Narrative reviews, comments, opinion papers, editorials, letters or any other publication lacking primary data and/or explicit method descriptions, were also excluded.

2.3. Data extraction

Data abstracted from the eligible studies were: i) first author's name; ii) year of publication; iii) study location; iv) study design; v) main inclusion criteria and underlying disease; vi) type of intervention; vii) study groups; vii) number of participants in the active and control groups; viii) maternal and ix) gestational age at base-line. Missing or unpublished data were sought by trying to contact authors or sponsors *via* e-mail and repeated messages were sent in case of no response. All data extraction and database typing were reviewed by the principal investigator (AFGC) before the final analysis, and doubts were resolved by mutual agreement among the authors.

2.4. Quality assessment

A systematic assessment of risk of bias in the included studies was performed using the Cochrane criteria risk of bias tool [12]. The following items were used: adequacy of sequence generation, allocation concealment, blinding addressing of dropouts (incomplete outcome data), selective outcome reporting, and other probable sources of bias [13]. Risk-of-bias assessment was independently performed by 2 authors (FF and AFGC); disagreements were resolved by a consensus-based discussion.

2.5. Data synthesis

Meta-analysis was entirely conducted using Comprehensive Meta-Analysis (CMA) V3 software (Biostat, NJ) [14]. Effect size was expressed as odd ratio (OR) and 95% CI [15]. Studies' findings were combined using a fixed-effect model since the low level of heterogeneity, which was quantitatively assessed using the Higgins index (I^2) [16]. When results were presented in multiple time points, only data relating to the longest duration of treatment were considered. Furthermore, in order to avoid a double-counting problem, in trials comparing multiple treatment arms versus a single control group, the number of subjects in the control group was divided by the required comparisons. Studies with zero events in both arms were excluded.

In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the leave-oneout method (i.e. removing one study at a time and repeating the analysis) [17].

Subgroup analyses were performed to explore the impact on the effect size of the beginning of the supplementation related to the gestational age (\leq 20 weeks or >20 weeks), whether the supplementation lasted up to the delivery and the impact of calcium intake and study blindness. Finally, as potential confounders of the treatment response, vitamin D biweekly supplemented dose and maternal age were entered into a fixed-effect meta-regression model to explore their association with the estimated effect size on the risk of preeclampsia. Two-sided *p*-values \leq 0.05 were considered statistically significant for all tests.

2.6. Publication bias

Potential publication biases were explored using visual inspection of Begg's funnel plot asymmetry, Begg's rank correlation test and Egger's weighted regression test [18,19]. The Duval & Tweedie "trim and fill" method was used to adjust the analysis for the effects of publication biases [20]. Two-sided *p* values \leq 0.05 were always considered as statistically significant and, in case of a significant result, Rosenthal fail-safe N test was applied in order to calculate the number of additional negative studies that would be needed to increase the *p* value for the meta-analysis to above 0.05 [21].

3. Results

3.1. Flow and characteristics of the included studies

After database searches performed strictly according to inclusion and exclusion criteria, 257 published articles were identified, and the abstracts were reviewed. Of these, 151 were excluded because they were non-original articles. Another 59 were eliminated because they did not finally meet the inclusion criteria. Thus, 47 articles were carefully assessed and reviewed. An additional 20 studies were excluded because of substantial sample overlap (n = 6), studies testing multivitamin or multimineral supplements with vitamin D (n = 3), or lack of a control group for vitamin D supplementation (n = 11) (Appendix 1).

Finally, 27 RCTs were eligible and included in the meta-analysis [22–48]. The study selection process is shown in Fig. 1. Data were pooled from 27 RCTs comprising 59 arms, which included 4777 participants, with 2487 in the vitamin D-treated arm and 2290 in the control one.

Eligible studies were published between 1980 and 2018 and enrolled pregnant women at low-to-high risk for preeclampsia according to the most recent guidelines of the European Society of Cardiology (ESC), the American Heart Association (AHA), and the American College of Obstetricians and Gynecologists (ACOG) [49–51]. They were conducted in Iran (n = 15), India (n = 3), Bangladesh (n = 2), France (n = 2), Brazil (n = 1), China (n = 1),



Fig. 1. Flow chart of the number of studies identified and included into the meta-analysis.

First author (year)	Study location	Design	Main inclusion criteria for the studies	Intervention	Study group	Participants (n)	Maternal age (years)	Gestational age (weeks)
Jamilian, M (2018) [22]	Iran	Randomized, double-blind, placebo-controlled, parallel- group, clinical trial	- Aged 18–40 years -primigravida women - 24–28 weeks of	Vitamin D	Vitamin D ₃ 50 000 IU and probiotics once every two weeks	30	28.9 ± 6.1	NA
			gestation - diagnosis of gestational diabetes mellitus		Probiotics	30	31.2 ± 5.9	NA
Sasan, SB (2017) [23]	Iran	Randomized, double-blind, placebo-controlled, parallel- group, clinical study	- History of preeclampsia in previous pregnancies	Vitamin D	Vitamin D ₃ 50 000 IU once every two weeks Placebo	70 72	32 ± 5.9 298 + 52	14.4 ± 3.1 14.4 ± 2.7
			- serum 25-OH vitamin $D \ge 25 \text{ ng/ml}$	× #.		22	25.0 ± 5.2	14.4 ± 2.7
[24]	Iran	Randomized, double-blind, placebo-controlled, parallel- group, clinical study	 Aged 18-40 years singleton pregnancy 25 weeks of gestation 	D + Calcium	$D_3 200 IU/$ day + Calcium 500 mg/day Placebo	23	25.7 ± 4.2 24.3 + 3.4	NA
Cooper, C (2016)	United	Multicentre, randomized,	- Age > 18 years	Vitamin D	Vitamin D ₃ 1000 IU/day	565	30.5 + 5.2	NA
[25]	Kingdom	double-blind, placebo-	- singleton pregnancy		Placebo	569	30.5 ± 5.2	NA
	5	controlled, parallel-group, clinical trial	- <17 weeks of gestation		Vitamin D ₃ 2000 IU/day	86	26 (22 -33) ^a	27 (26 –29) ^a
					Placebo	87	28 (23	27 (26
							$-33)^{a}$	$-29)^{a}$
Vaziri, F (2016)	Iran	Randomized, double-blind,	- Age \geq 18 years	Vitamin D	Vitamin D ₃ 2000 IU/day	78	26.4 ± 4.88	NA
[26]		placebo-controlled, parallel-	 singleton pregnancy 		Placebo	75	26.2 ± 4.3	NA
		group, clinical trial	- 26–28 weeks of gestation		Vitamin D ₃ 2000 IU/day	86	29 ± 6	27 (26 -30) ^a
			- no previous cesarean sections		Placebo	87	30 ± 6	27 (26 —29) ^a
Yazdchi, R (2016) [27]	Iran	Randomized, double-blind, placebo-controlled, parallel-	- Age 15–45 years - 24–28 weeks of	Vitamin D	Vitamin D ₃ 50 000 IU once every two weeks	38	31.6 ± 4.4	NA
		group, clinical trial	gestation - diagnosis of gestational diabetes mellitus		Placebo	38	32.1 ± 3.6	NA
Karamali, M (2015) <mark>[28]</mark>	Iran	Randomized, double-blind, placebo-controlled, parallel-	- Age 18—40 years - primigravida women	Vitamin D	Vitamin D ₃ 50 000 IU once every two weeks	30	27.4 ± 5.2	NA
		group, clinical trial	- women at risk for preeclampsia		Placebo	30	27.4 ± 5.2	NA
[29] [29]	China	Randomized, double-blind, placebo-controlled, parallel- group, clinical trial	 Age 20–32 years nulliparous woman singleton pregnancy 18–20 weeks of gestation 	Vitamin D	Vitamin D₃ 2000 IU/day Placebo	30 30	NA NA	NA NA
Mohammad-	Iran	Randomized, triple-blind,	- Age 18–39 years	Vitamin D	Vitamin D ₃ 1000 IU/day	42	27.7 ± 5.6	NA
Alizadeh- Charandabi, S		placebo-controlled, parallel- group, clinical trial	- 25–30 weeks of gestation	and Vitamin D + Calcium	Vitamin D ₃ 1000 IU/ day + Calcium 300 mg/day	42	27.5 ± 5.3	NA
(2015) [30]		•	0		Placebo	42	26.4 ± 4.9	NA
Sablok, Á (2015) [31]	India	Randomized controlled trial	 Primigravida woman singleton pregnancy 14–20 weeks of gestation 	Vitamin D	Vitamin D ₃ 60 000 IU once at 20 weeks of gestation Vitamin D ₃ 120 000 IU at 20 and 24 weeks of gestation Vitamin D ₃ 120 000 IU at 20, 24, 28 and 32 weeks of gestation No intervention	60	NA	NA
Samimi, M (2015) [32]	Iran	Randomized, double-blind, placebo-controlled, parallel- group, clinical trial	 Age 18–40 years primigravida women women at risk for preeclampsia 	Vitamin D + Calcium	Vitamin D ₃ 50 000 IU every two weeks + Calcium 1000 mg/day Placebo	30	27.3 ± 3.7 27.1 ± 5.2	NA
Shahgheibi. S	Iran	Randomized, double-blind	- At least one risk factor	Vitamin D ₂	Vitamin D ₃ 5000 IU/dav	50	NA	NA
(2015) [33]	•	placebo-controlled, parallel- group, clinical trial	for gestational diabetes mellitus	D3	Placebo	50	NA	NA
Asemi, Z (2014) [34]	Iran	Randomized, double-blind, placebo-controlled, parallel- group, clinical trial	 Age 18–40 years diagnosis of gestational diabetes 	Vitamin D + Calcium	Vitamin D ₃ 50 000 IU at study baseline and on day 21 + Calcium 1000 mg/day	28	28.7 ± 6.0	NA
			mellitus at 24–28 weeks of gestation - no insulin therapy		Placebo	28	30.8 ± 6.6	NA
Grant, CC (2014) [35]	New Zealand	Randomized, double-blind, placebo-controlled, parallel-	 - >27-weeks of gestation 	Vitamin D	Vitamin D ₃ 1000 IU/day	87	27 ± 6	28 (26 –29) ^a
- •		group, clinical trial	- singleton pregnancy		Vitamin D ₃ 2000 IU/day	86	26 ± 6	27 (26 –29) ^a
					Placebo	87	28 ± 6	27 (26 –29) ^a

(continued on next page)

First author (year)	Study location	Design	Main inclusion criteria for the studies	Intervention	Study group	Participants (n)	Maternal age (years)	Gestational age (weeks)
Harrington, J (2014) [36]	Bangladesh	Randomized, double-blind, placebo-controlled, parallel-	- Third trimester of gestation	Vitamin D	Vitamin D ₃ 35 000 IU once every week	80	NA	NA
		group clinical study	1 1 1 0 1 0		Placebo	80	NA	NA
Asemi, Z (2013)	Iran	Randomized, double-blind,	- Aged 18–40 years	Vitamin D	Vitamin D ₃ 400 IU/day	27	25.3 ± 4.2	NA
[37]		group, clinical trial	- 25 weeks of gestation			27	24.8 ± 3.6	NA
Asemi, Z (2013) [38]	Iran	Randomized, double-blind, placebo-controlled, parallel- group, clinical trial	 Aged 18–40 years diagnosis of gestational diabetes 	D + Calcium	Vitamin D_3 IU 50 000 IU at study baseline and on day 21 + Calcium 1000 mg/day	27	31.7 ± 5.6	NA
			mellitus at 24–28 weeks of gestation		Placebo	27	31.8 ± 6.6	NA
Diogenes, ME (2013) [39]	Brazil	Randomized, single-blind, placebo-controlled, parallel-	 Age 13–19 years primigravida women 	Vitamin D + Calcium	Vitamin D ₃ 200 IU/ day + Calcium 600 mg/day	43	NA	NA
		group, clinical trial	 singleton pregnancy 23–29 weeks of gestation 		Placebo	41	NA	NA
Jelsma, JG (2013)	Europe	Multicentre Europe-wide,	- Age \geq 18 years	Vitamin D	Vitamin D ₃ 1600 IU/day	110	NA	NA
[40]		randomized, single-blind, placebo-controlled, clinical trial	 BMI ≥ 29 kg/m² singleton pregnancy ≤19 weeks and 6 days of gestation 		Placebo	110	NA	NA
Naghshineh, E	Iran	Randomized, double-blind,	- Nulliparous women	Vitamin D	Vitamin D ₃ 600 IU/day	70	25 ± 4.1	NA
(2013) [41]		placebo-controlled, parallel- group, clinical trial	- <16 weeks of gestation		Placebo	70	25 ± 4.1	NA
Roth, DE (2013) [42]	Bangladesh	Randomized, double-blind, placebo-controlled, parallel-	- Age 18–35 years - 26–30 weeks of	Vitamin D	Vitamin D ₃ 35 000 IU once every week	80	22.4 ± 3.5	27.6 ± 1.1
		group, clinical trial	gestation		Placebo	80	22.4 ± 3.4	27.9 ± 1.0
Asemi, Z (2012) [43]	Iran	Randomized, single-blind, placebo-controlled, parallel-	 Age 18–35 years primigravida women 	Vitamin D + Calcium	Vitamin D ₃ 200 IU/ day + Calcium 500 mg/day	24	24.9 ± 4.2	NA
		group, clinical trial	 singleton pregnancy women at risk for preeclampsia third trimester of gestation 		Placedo	25	24.9 ± 3.7	NA
Taherian AA (2002) [44]	Iran	Randomized controlled trial	 Nulliparous woman singleton pregnancy 	Vitamin D + Calcium	Vitamin D ₃ 200 IU/ day + Calcium 500 mg/day	330	21.9 (21.6 -22.4) ^a	NA
			 - <20 weeks of gestation - SBP/DBP ≤ 130/ 80 mmHg and no proteinuria detectable 		No treatment	330	21.2 (20.8 -21.6) ^a	NA
			by a dipstick					
Marya, RK (1987) <mark>[45]</mark>	India	Randomized controlled trial	- Age 20—35 years	Vitamin D + Calcium	Vitamin D ₃ 1200 IU/ day + Calcium 375 mg/day	200	NA	NA
					No treatment	200	NA	NA
Delvin, EE (1986)	France	Randomized, double-blind,	- Singleton pregnancy	Vitamin D	Vitamin D ₃ 1000 IU/day	40	NA	NA
[46]		placebo-controlled, parallel- group, clinical trial	 third trimester of pregnancy 	r.	Placebo	40	NA	NA
Mallet, E (1986) [47]	France	Randomized controlled trial	- Third trimester of pregnancy in winter	Vitamin D	Vitamin D ₂ 1000 IU/day	21	26 (18 -35) ^b	NA
					Vitamin D ₂ 200 000 IU	27	25 (19 -36) ^b	NA
					No treatment	29	25 (18 -35) ^b	NA
Brooke, OG	India	Randomized, double-blind,	- Asian ethnicity	Vitamin D	Vitamin D ₃ 1000 IU/day	59	23.9 ± 4.8	NA
(1980) [48]		placebo-controlled, parallel- group, clinical trial			Placebo	67	23.7 ± 3.1	NA

DBP = Diastolic blood pressure; NA = Not available; SBP = Systolic blood pressure.

^a Expressed as median and (95% confidence interval).

^b Expressed as mean and variation range.

Europe (multicentre Europe-wide study) (n = 1), New Zealand (n = 1), and United Kingdom (n = 1). Several pharmaceutical forms of vitamin D and different timings of administration were tested across the studies. Detailed baseline characteristics of the evaluated studies are summarized in Table 1.

3.2. Risk of bias assessment

Almost every included study was characterized by sufficient information regarding random sequence generation, allocation concealment and personnel blinding, and outcome assessments, and showed low risk of bias because of incomplete outcome data and selective outcome reporting. Details of the quality of bias assessment are reported in Table 2.

3.3. Risk of preeclampsia

No cases of preeclampsia were experienced by pregnant women enrolled in 17 studies among those selected. In pooled analyses for the remaining 12 studies, vitamin D supplementation was inversely associated with an increased risk of preeclampsia (OR 0.37, 95% CI: 0.26, 0.52, p < 0.001; $l^2 = 0\%$) (Fig. 2) and the results remained

Table 2	ble 2
---------	-------

Quality of bias assessment of the included studies according to Cochrane guidelines.

First author (year)	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Jamilian, M (2018) [22]	L	L	L	L	L	L
Sasan, SB (2017) [23]	L	L	L	L	L	L
Asemi, Z (2016) [24]	L	L	L	L	L	L
Cooper, C (2016) [25]	L	L	L	L	L	L
Vaziri, F (2016) [26]	L	L	L	L	L	L
Yazdchi, R (2016) [27]	L	L	L	L	L	L
Karamali, M (2015) [28]	L	L	L	L	L	L
Lei, Q (2015) [29]	L	L	L	L	L	L
Mohammad-Alizadeh-	L	L	L	L	L	L
Charandabi, S (2015) [30]						
Sablok, A (2015) [31]	Н	Н	Н	L	L	U
Samimi, M (2015) [32]	L	L	L	L	L	L
Shahgheibi, S (2015) [33]	L	L	L	L	L	L
Asemi, Z (2014) [34]	L	L	L	L	L	L
Grant, CC (2014) [35]	L	L	L	L	L	L
Harrington, J (2014) [36]	L	L	L	L	L	L
Asemi, Z (2013 a) [37]	L	L	L	L	L	L
Asemi, Z (2013 b) [38]	L	L	L	L	L	L
Diogenes, ME (2013) [39]	Н	Н	U	L	L	L
Jelsma, JG (2013) [40]	U	U	U	L	L	L
Naghshineh, E (2013) [41]	L	L	L	L	L	L
Roth, DE (2013) [42]	L	L	L	L	L	L
Asemi, Z (2012) [43]	Н	Н	U	L	L	L
Taherian AA (2002) [44]	Н	Н	Н	L	L	U
Marya, RK (1987) [45]	Н	Н	Н	L	L	U
Delvin, EE (1986) [46]	L	L	L	Н	U	L
Mallet, E (1986) [47]	Н	Н	Н	L	L	U
Brooke, OG (1980) [48]	L	L	L	Н	U	L

L = Low risk of bias; H = High risk of bias; U = Unclear risk of bias.

strong in the leave-one-out sensitivity analysis (Fig. S1). When the supplementation began up to 20 weeks of gestation, the risk was even a little lower (OR 0.35, 95% CI: 0.24, 0.50, p < 0.001; $l^2 = 0$ %). When the supplementation of vitamin D was started after the 20th week, the statistical significance was lost, though the trend was maintained (OR 0.60, 95% CI: 0.18, 2.03, p = 0.411; $l^2 = 0$ %). The test to compare the two effect sizes (0.35 *vs* 0.60) yielded a Q-value of 0.69 with a corresponding *p* value of 0.408, so that there were no significant differences between groups.

The effect was largely independent from the continuity of the supplementation before (OR 0.36, 95% CI: 0.23, 0.55, p < 0.001; $l^2 = 0\%$) or up to delivery (OR 0.38, 95% CI: 0.21, 0.69, p = 0.002; $l^2 = 0\%$) (p between groups 0.877), from the type of intervention considering vitamin D alone (OR 0.37, 95% CI: 0.24, 0.56, p < 0.001; $l^2 = 0\%$) or in association with calcium (OR 0.36, 95% CI: 0.20, 0.67, p = 0.001; $l^2 = 0\%$) (p between groups 0.966) and whether openlabel (OR 0.34, 95% CI: 0.21, 0.55, p < 0.001; $l^2 = 0\%$) or blinded (OR 0.40, 95% CI: 0.23, 0.56, p < 0.001; $l^2 = 0\%$) (p between groups 0.966) and whether openlabel (OR 0.40, 95% CI: 0.23, 0.56, p < 0.001; $l^2 = 0\%$) (p between groups 0.966) and whether openlabel (OR 0.40, 95% CI: 0.23, 0.56, p < 0.001; $l^2 = 0\%$) (p between groups 0.966) and whether openlabel (OR 0.40, 95% CI: 0.23, 0.56, p < 0.001; $l^2 = 0\%$) (p between groups 0.966) and whether openlabel (OR 0.40, 95% CI: 0.23, 0.56, p < 0.001; $l^2 = 0\%$) (p between groups 0.966) and whether openlabel (OR 0.40, 95% CI: 0.23, 0.56, p < 0.001; $l^2 = 0\%$) (p between groups 0.966) and whether openlabel (OR 0.40, 95% CI: 0.23, 0.56, p < 0.001; $l^2 = 0\%$) (p between groups 0.966) and whether openlabel (OR 0.40, 95% CI: 0.23, 0.56, p < 0.001; $l^2 = 0\%$) (p between groups 0.966) and whether openlabel (OR 0.40, 95% CI: 0.23, 0.56, p < 0.001; $l^2 = 0\%$) (p between groups 0.966) and whether openlabel (OR 0.40, 95% CI: 0.23, 0.56, p < 0.001; $l^2 = 0\%$) (p between groups 0.966) and whether openlabel (P = 0.001; P =

Study name		Statist	ics for e	ach study		Events	/ Total		Odds rat	io and 95% (
	Odds ratio	Lower	Upper limit	Z-Value	p-Value	Vitamin D	Control			
Jamilian, M (2018)	0,643	0,100	4,153	-0,464	0,643	2/30	3 / 30	1		+
Sasan, SB (2017)	0,424	0,187	0,958	-2,063	0,039	11 / 70	22 / 72			-
Asemi, Z (2016)	0,319	0,012	8,251	-0,688	0,491	0/23	1/23			
Karamali, M (2015)	0,310	0,030	3,168	-0,987	0,324	1/30	3 / 30	-		+
Lei, Q (2015)	0,327	0,104	1,032	-1,908	0,057	6/30	13 / 30		-	-
Sablok, A (2015)	0,314	0,158	0,627	-3,284	0,001	22 / 120	25 / 60			
Samimi, M (2015)	0,310	0,030	3,168	-0,987	0,324	1/30	3 / 30			
Asemi, Z (2013a)	0.321	0,013	8,241	-0,686	0,493	0 / 27	1 / 27			-
Asemi, Z (2013b)	0,321	0,013	8,241	-0,686	0,493	0 / 27	1 / 27	-		-
Naghshineh, E (2013)	0,265	0,053	1,322	-1,620	0,105	2/70	7 / 70			+
Roth, DE (2013)	3,038	0,122	75,693	0,677	0,498	1 / 80	0 / 80			+ •
aherian AA (2002)	0,369	0,191	0,715	-2,955	0,003	13 / 330	33 / 330			
	0,385	0,257	0,519	-5,612	0,000				-	1

Favours Vitamin D Favours Control

Fig. 2. Forest plot comparing the risk of preeclampsia in the studied groups.



Favours Vitamin D Favours Control

Group by	Study name		Statist	ics for e	ach study			Odd	Is ratio and 95% Cl	
Supplementation until delivery		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value				
No	Jamilian, M (2018)	0,643	0.100	4,153	-0.464	0.643	1	-		1
No	Sasan, SB (2017)	0,424	0,187	0,958	-2.063	0.039		-	-	
No	Asemi, Z (2016)	0.319	0,012	8,251	-0.688	0.491		_		
No	Karamali. M(2015)	0.310	0.030	3,168	-0.987	0.324	-	_		
No	Lei, Q (2015)	0.327	0.104	1,032	-1,906	0.057		-	-	
No	Sablok, A (2015)	0.314	0,158	0.627	-3.284	0,001			•	
No	Samimi, M(2015)	0,310	0.030	3,168	-0.987	0,324		_		
No	Asemi, Z (2013a)	0.321	0.013	8.241	-0.686	0.493		_		
No	Asemi, Z (2013b)	0.321	0.013	8,241	-0.686	0.493		_		
No		0,358	0.232	0,552	-4,637	0,000				
Yes	Naghshineh, E (2013)	0.265	0.053	1.322	-1.620	0.105		-		
Yes	Roth. DE (2013)	3.038	0.122	75.693	0.677	0.498				-1
Yes	Taherian AA (2002)	0.369	0.191	0.715	-2,955	0.003		_	a	
Yes		0,379	0.208	0.691	-3,164	0.002			<u> </u>	
Ov erall		0.365	0.257	0,519	-5,612	0.000			l	
							0.01	0.1	1 10	100

Favours Vitamin D Favours Control

Group by	Study name		Statist	ics for e	ach study	<u>.</u>		Odds rat	io and 95%Cl
Intervention		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value			
Calcium + Vitamin D	Asemi, Z (2016)	0,319	0,012	8,251	-0,688	0,491	1	+ •	+
Calcium + Vitamin D	Samini, M (2015)	0,310	0,030	3,168	-0,987	0,324	1.7		
Calcium + Vitamin D	Asemi, Z (2013b)	0,321	0,013	8,241	-0,686	0,493		· ·	
Calcium + Vitamin D	Taherian AA (2002)	0,369	0,191	0,715	-2,965	0,003			-
Calcium + Vitamin D		0,361	0,196	0,666	-3,259	0,001			
Vitamin D	Jamilian, M (2018)	0,643	0,100	4,153	-0,464	0,643		-	-
Vitamin D	Sasan, SB (2017)	0,424	0,187	0,958	-2,063	0,039			-
Vitamin D	Karamali, M (2015)	0,310	0,030	3,168	-0,987	0,324	2 		<u> </u>
Vitamin D	Lei, Q (2015)	0,327	0,104	1,032	-1,906	0,057			-
Vitamin D	Sablok, A (2015)	0,314	0,158	0,627	-3,284	0,001			
Vitamin D	Asemi, Z (2013a)	0,321	0,013	8,241	-0,686	0,493			
Vitamin D	Naghshineh, E (2013)	0,265	0,053	1,322	-1,620	0,105			+
Vitamin D	Roth, DE (2013)	3,038	0,122	75,693	0,677	0,498			
Vitamin D		0,367	0,239	0,564	-4,568	0,000		-	
Overall		0,365	0.257	0,519	-5,612	0,000		-	1
							0,01	0,1	1

Favours Vitamin D Favours Control

Group by Study name Statistics for each study Odds ratio and 95%Cl Odds Upper Z-Value p-Value ratio limit limit Blind Jamilian, M(2018) 0,643 0,100 4,153 -0,464 0.643 Blind Sasan, SB (2017) 0,424 -2.063 0,039 0.958 0,187 Blind Asemi, Z (2016) 0,319 8,251 -0.688 0.012 0.491 Blind Karamali, M(2015) 0,310 0.030 3.168 -0,987 0,324 Lei, Q (2015) 0,327 0,057 Blind 0,104 1,032 -1,906 Blind Samimi, M(2015) 0,310 0,030 3,168 -0,987 0,324 Asemi, Z (2013a) 0,321 0,013 Blind 8,241 -0,686 0,493 Blind Asemi, Z (2013b) 0,321 0,013 8,241 -0,686 0,493 Blind Naghshineh, E (2013) 0,265 0,053 1,322 -1,620 0,105 Blind Roth, DE (2013) 3,038 0.122 75,693 0,677 0,498 Blind 0,395 0,234 0,664 -3,499 0,000 Open-label Sablok, A(2015) 0,314 0,158 0,627 -3,284 0,001 Open-label Taherian AA (2002) 0,369 0,191 0,715 -2.955 0,003 Open-label 0,342 0,212 0.551 -4.406 0,000 Overall 0,365 0,257 0.519 -5.612 0.000



Fig. 3. Forest plot displaying the risk of preeclampsia in the studied groups. Subgroup analyses stratified by timing for the supplementation, the type of intervention and the study design.





Vitamin D (IU/2weeks)





Maternal age

Fig. 4. Meta-regression bubble plots of the association between log odds ratio and vitamin D dosage (above) and maternal age (below). The size of each circle is inversely proportional to the variance of change.

0.690) (Fig. 3). Increasing the dosage of vitamin D was inversely associated with the increasing risk of preeclampsia (slope of *log* OR: -1.1, 95% CI: -1.73, -0.46, corresponding to OR 0.33, 95% CI: 0.18, 0.63; two-tailed p < 0.001) (Fig. 4). This risk of preeclampsia was not associated with maternal age (p > 0.05) (Fig. 4).

Visually, the funnel plot of standard error by log odds ratio was slightly asymmetric (Fig. S2). This asymmetry was imputed to two potentially missing studies on the right side of the funnel plot, which altered the estimated risk of preeclampsia from 0.365 to 0.373 (95% CI: 0.265, 0.524). However, Egger's linear regression and Begg's rank correlation did not confirm the presence of any publication bias (p > 0.05 for all comparisons). Finally, the classic failsafe N test suggested that 52 studies with negative results would be needed to bring the estimated risk of preeclampsia to a nonsignificant level (p > 0.05).

4. Discussion

Preeclampsia is associated with adverse maternal and fetal outcomes [52,53], hence there is an increasing urgency in identifying clinical and laboratory predictors of preeclampsia, though it is even more important to identify safe and effective ways to prevent its development. To the best of our knowledge, the current systematic review and meta-analysis is the first to comprehensively analyze evidence from randomized controlled clinical studies on the efficacy of supplementation with vitamin D on the prevention of preeclampsia.

A previous meta-analysis by Khaing et al. mainly focused on calcium supplementation, concluded that vitamin D supplementation might also have been beneficial for the prevention of hypertensive disorders in pregnancy, though more evidence was needed [54]. However, our meta-analysis would be large enough to dispel any doubt. On the basis of the present findings, vitamin D supplementation was very beneficial in prevention of preeclampsia and largely independent of the timing of the supplementation (until delivery or not), maternal age and vitamin D dosage. When the supplementation is started up to 20 weeks of gestation, the benefit for pregnant women seems to be much higher.

Furthermore, co-administration of vitamin D combined with calcium does not seem to bring an additional benefit. On the other hand, calcium requires daily administration and a high dosage, that could increase the general cardiovascular risk of the pregnant women [55,56]. Indeed, the most recent ESC, World Health Organization (WHO) and ACOG Guidelines [49,51,57] recommend calcium supplementation to be prescribed in deficiency in the pregestational age without referring to vitamin D, although the latter might be preferred for preventing preeclampsia. Indeed, vitamin D deficiency is associated with a relatively large number of risk factors for endothelial dysfunction and vascular health impairment [58]. On the other side, adequate vitamin D intake might help with the maintenance of the calcium homeostasis – which is inversely related to blood pressure levels - [32] or may directly suppress the proliferation of the vascular smooth muscle cells [59]. Furthermore, vitamin D might be a powerful endocrine suppressor of renin biosynthesis and could regulate the renin-angiotensin system, which plays a critical role in blood pressure control [59]. Finally, vitamin D could also modulate the synthesis of adipokines related to endothelial and vascular health [60].

There are some limitations of the current analysis. The main one is related to the different administration timing and pharmaceutical forms of vitamin D supplemented to the pregnant women. At a high dosage, even in a single administration, vitamin D may therefore be sufficient to prevent preeclampsia, considering that vitamin D accumulates in body fat [61]. Further research should be focused on the recommended regimen in pregnancy (i.e. daily, weekly or a single dose). Based on our data we might recommend beginning of a supplementation up to 20 week of a pregnancy, irrespective it is going to be continued up to delivery or not, with the dose around 25.000 UI/week, where the weekly administration could require the monitoring of calcemia and calciuria as potentially markers of potential vitamin D overdose. Thought it seems to be no interaction between vitamin D and preeclampsia by maternal age, the explored range of age in our meta-analysis is narrow since the included studies do not enroll women younger than 20 or older than 34 years. Then, in the included RCTs, no information on achieved vitamin D serum level is reported. As a result, it is still unknown if the benefit of vitamin D supplementation is greater among women still with vitamin D deficiency and/or in the ones reaching the optimal serum vitamin D levels. However, the aim of our study was to evaluate if clinical vitamin D supplementation per se could prevent a clinically relevant outcome such as preeclampsia incidence and our results confirm this hypothesis. Moreover, our positive results could also underestimate the potential preventive effect of vitamin D supplementation, since the most part of enrolled patients were not strictly selected based on their baseline circulating vitamin D nor their achievement of optimal vitamin D after supplementation. Studies from North America and Africa are also not available and this is of particular importance since prevalence of 25(OH)-vitamin D deficiency differs in various parts of the world based on latitude and sociocultural practices such as covered manner of dress for women [62,63]. Thus, our data could not automatically inferred to North-American and African women. even if we could suppose that the mechanisms potentially involved in the protective effect of vitamin D towards preeclampsia incidence are similar in all ethnicities [63–65].

The main strength of this meta-analysis is the number of the studies included and the low degree of heterogeneity observed. Our meta-analysis might have also important clinical relevance as it indicates that vitamin D supplementation may prevent preeclampsia. For that reason, it should be especially considered in pregnant women at increased risk of developing hypertensive disorders, mostly in countries with a high risk for vitamin D deficiency, including most of the European and some Asian countries [62–65]. This is relevant since in the most recent guidelines, vitamin D supplementation is not taken into consideration for preeclampsia prevention [49,50,57].

5. Conclusions

In conclusion, vitamin D supplementation may be useful in preventing preeclampsia. Large, well-designed prospective randomized clinical trials are needed to definitively address vitamin D supplementation as a possible intervention strategy and in order to identify the most effective dose regimen.

Authors' contribution

Silvia Fogacci and Federica Fogacci conceived, designed and performed the analysis; Maciej Banach and Arrigo F.G. Cicero verified the analytical methods; Silvia Fogacci, Federica Fogacci, Maciej Banach and Arrigo F.G. Cicero wrote the paper; Michael J. Blaha, Silvia Fogacci, Adrian V. Hernandez, Gregory Y.H. Lip, Erin D. Michos and Peter P. Toth provided critical revision of the manuscript; all Authors discussed the results and contributed to the final manuscript.

Funding

The present paper was written independently; no company or institution supported it financially. No professional writer was involved in the preparation of this meta-analysis.

Conflict of interest

Maciej Banach has served on the speakers bureau of Abbott/ Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi-Aventis, Servier and Valeant, has served as a consultant to Abbott Vascular, Akcea, Amgen, Daichii Sankyo, Esperion, Lilly, MSD, Resverlogix, Sanofi-Aventis, and has received grants from Sanofi and Valeant; *Claudio Borghi* has served as a consultant to Menarini and Servier; *Arrigo F.G. Cicero* has given talks, furnished scientific consultancies and/or participated in trials sponsored by Amgen, Angelini, Menarini and Mylan; *Federica Fogacci* has served as a consultant to Mylan; *Peter P. Toth* is a speaker and/or consultant for Amarin, Amgen, AstraZeneca, Kowa, Novo-Nordisk, Regeneron, Resverlogix, and Sanofi; *Michael J. Blaha, Silvia Fogacci, Adrian V. Hernandez, Gregory Y.H. Lip* and *Erin D. Michos* have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.08.015.

References

- [1] Wheeler BJ, Taylor BJ, de Lange M, Harper MJ, Jones S, Mekhail A, et al. A longitudinal study of 25-hydroxy vitamin D and parathyroid hormone status throughout pregnancy and exclusive lactation in New Zealand mothers and their infants at 45° S. Nutrients 2018;10:E86. https://doi.org/10.3390/ nu10010086.
- [2] Karras SN, Wagner CL, Angeloudi E, Kotsa K. Maternal vitamin D status during pregnancy in Europe: the two sides of the story. Eur J Nutr 2017;56:2207–8. https://doi.org/10.1007/s00394-017-1451-x.
- [3] Heyden EL, Wimalawansa SJ. Vitamin D: effects on human reproduction, pregnancy, and fetal well-being. J Steroid Biochem Mol Biol 2018;180:41–50. https://doi.org/10.1016/j.jsbmb.2017.12.011.
- [4] Koster MPH, van Duijn L, Krul-Poel YHM, Laven JS, Helbing WA, Simsek S, et al. A compromised maternal vitamin D status is associated with congenital heart defects in offspring. Early Hum Dev 2018;117:50–6. https://doi.org/10.1016/ j.earlhumdev.2017.12.011.
- [5] Sparling TM, Nesbitt RC, Henschke N, Gabrysch S. Nutrients and perinatal depression: a systematic review. J Nutr Sci 2017;6:e61. https://doi.org/ 10.1017/jns.2017.58.
- [6] Lepsch J, Eshriqui I, Farias DR, Vas JS, Cunha Figueiredo AC, Adegboye AR, et al. Association between early pregnancy vitamin D status and changes in serum lipid profiles throughout pregnancy. Metabolism 2017;70:85–97. https:// doi.org/10.1016/j.metabol.2017.02.004.
- [7] Serrano-Díaz NC, Gamboa-Delgado EM, Domínguez-Urrego CL, Vesga-Varela AL, Serrano-Gómez SE, Quintero-Lesmes DC. Vitamin D and risk of preeclampsia: a systematic review and meta-analysis. Biomedica 2018;38: 43–53. https://doi.org/10.7705/biomedica.v38i0.3683.
- [8] Zhao X, Fang R, Yu R, Chen D, Zhao J, Xiao J. Maternal vitamin D status in the late second trimester and the risk of severe preeclampsia in Southeastern China. Nutrients 2017;9. https://doi.org/10.3390/nu9020138. pii: E138.
- [9] Shi DD, Wang Y, Guo JJ, Zhou L, Wang N. Vitamin D enhances efficacy of oral nifedipine in treating preeclampsia with severe features: a double blinded, placebo-controlled and randomized clinical trial. Front Pharmacol 2017;8: 865. https://doi.org/10.3389/fphar.2017.00865.
- [10] Purswani JM, Gala P, Dwarkanath P, Larkin HM, Kurpad A, Mehta S. The role of vitamin D in pre-eclampsia: a systematic review. BMC Pregnancy Childbirth 2017;17:231. https://doi.org/10.1186/s12884-017-1408-3.
- [11] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535. https://doi.org/10.1136/bmj.b2535.
- [12] Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.0. 2. 2009. Chichester, UK: John Wiley and Sons Ltd; 2010. Ref Type: Report.
- [13] Fogacci F, Banach M, Mikhailidis DP, Bruckert E, Toth PP, Watts GF, et al. Safety of red yeast rice supplementation: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2019;143:1–16. https://doi.org/ 10.1016/j.phrs.2019.02.028.
- [14] Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive meta-analysis version 3, vol. 104. Englewood, NJ: Biostat; 2005.
- [15] Haenszel W, Hon NB. Statistical approaches to the study of cancer with particular reference to case registers. J Chronic Dis 1956;4:589–99.
- [16] Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-

analyses. Clin Microbiol Infect 2014;20:123-9. https://doi.org/10.1111/1469-0691.12494.

- [17] Bown MJ, Sutton AJ. Quality control in systematic reviews and meta-analyses. Eur J Vasc Endovasc Surg 2010;40:669–77. https://doi.org/10.1016/ j.ejvs.2010.07.011.
- [18] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
- [19] Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53:1119–29.
- [20] Duval S, Tweedie R. Trim and fill: a simple funnel plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455-63.
- [21] Rosenthal R. The file drawer problem and tolerance for null results. Psychol Bull 1979;86:638-64. https://doi.org/10.1037/0033-2909.86.3.638.
- [22] Jamilian M, Amirani E, Asemi Z. The effects of vitamin D and probiotic cosupplementation on glucose homeostasis, inflammation, oxidative stress and pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebo-controlled trial. Clin Nutr 2019;38:2098–105.
- [23] Behjat Sasan S, Zandvakili F, Soufizadeh N, Baybordi E. The effects of vitamin D supplement on prevention of recurrence of preeclampsia in pregnant women with a history of preeclampsia. Obstet Gynecol Int 2017;2017:8249264. https://doi.org/10.1155/2017/8249264.
- [24] Asemi Z, Samimi M, Siavashani MA, Mazloomi M, Tabassi Z, Karamali M, et al. Calcium-vitamin D co-supplementation affects metabolic profiles, but not pregnancy outcomes, in healthy pregnant women. Int J Prev Med 2016;7:49. https://doi.org/10.4103/2008-7802.177895.
- [25] Cooper C, Harvey NC, Bishop NJ, Kennedy S, Papageorghiou AT, Schoenmakers I, et al. Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial. Lancet Diabetes Endocrinol 2016;4:393–402. https:// doi.org/10.1016/S2213-8587(16)00044-9.
- [26] Vaziri F, Nasiri S, Tavana Z, Dabbaghmanesh MH, Sharif F, Jafari P. A randomized controlled trial of vitamin D supplementation on perinatal depression: in Iranian pregnant mothers. BMC Pregnancy Childbirth 2016;16: 239. https://doi.org/10.1186/s12884-016-1024-7.
- [27] Yazdchi R, Gargari BP, Asghari-Jafarabadi M, Sahhaf F. Effects of vitamin D supplementation on metabolic indices and hs-CRP levels in gestational diabetes mellitus patients: a randomized, double-blinded, placebo-controlled clinical trial. Nutr Res Pract 2016;10:328–35. https://doi.org/10.4162/ nrp.2016.10.3.328.
- [28] Karamali M, Beihaghi E, Mohammadi AA, Asemi Z. Effects of high-dose vitamin D supplementation on metabolic status and pregnancy outcomes in pregnant women at risk for pre-eclampsia. Horm Metab Res 2015;47:867–72. https://doi.org/10.1055/s-0035-1548835.
- [29] Qian L, Wang H, Wu F, Li M, Chen W, Lv L. Vitamin D3 alters Toll-like receptor 4 signaling in monocytes of pregnant women at risk for preeclampsia. Int J Clin Exp Med 2015;8:18041–9.
- [30] Mohammad-Alizadeh-Charandabi S, Mirghafourvand M, Mansouri A, Najafi M, Khodabande F. The effect of vitamin D and calcium plus vitamin D during pregnancy on pregnancy and birth outcomes: a randomized controlled trial. J Caring Sci 2015;4:35–44. https://doi.org/10.5681/ jcs.2015.004.
- [31] Sablok A, Batra A, Thariani K, Batra A, Bharti R, Aggarwal AR, et al. Supplementation of vitamin D in pregnancy and its correlation with feto-maternal outcome. Clin Endocrinol 2015;83:536–41. https://doi.org/10.1111/ cen.12751.
- [32] Samimi M, Kashi M, Foroozanfard F, Karamali M, Bahmani F, Asemi Z, et al. The effects of vitamin D plus calcium supplementation on metabolic profiles, biomarkers of inflammation, oxidative stress and pregnancy outcomes in pregnant women at risk for pre-eclampsia. J Hum Nutr Diet 2016;29:505–15. https://doi.org/10.1111/jhn.12339.
- [33] Shahgheibi S, Farhadifar F, Pouya B. The effect of vitamin D supplementation on gestational diabetes in high-risk women: results from a randomized placebo-controlled trial. J Res Med Sci 2016;21:2.
- [34] Asemi Z, Karamali M, Esmaillzadeh A. Effects of calcium-vitamin D cosupplementation on glycaemic control, inflammation and oxidative stress in gestational diabetes: a randomised placebo-controlled trial. Diabetologia 2014;57:1798–806. https://doi.org/10.1007/s00125-014-3293-x.
- [35] Grant CC, Stewart AW, Scragg R, Milne T, Rowden J, Ekeroma A, et al. Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. Pediatrics 2014;133:e143–53. https://doi.org/10.1542/ peds.2013-2602.
- [36] Harrington J, Perumal N, Al Mahmud A, Baqui A, Roth DE. Vitamin D and fetalneonatal calcium homeostasis: findings from a randomized controlled trial of high-dose antenatal vitamin D supplementation. Pediatr Res 2014;76:302–9. https://doi.org/10.1038/pr.2014.83.
- [37] Asemi Z, Samimi M, Tabassi Z, Shakeri H, Esmaillzadeh A. Vitamin D supplementation affects serum high-sensitivity C-reactive protein, insulin resistance, and biomarkers of oxidative stress in pregnant women. J Nutr 2013;143:1432–8. https://doi.org/10.3945/jn.113.177550.
- [38] Asemi Z, Hashemi T, Karamali M, Samimi M, Esmaillzadeh A. Effects of vitamin D supplementation on glucose metabolism, lipid concentrations, inflammation, and oxidative stress in gestational diabetes: a double-blind randomized

controlled clinical trial. Am J Clin Nutr 2013;98:1425-32. https://doi.org/ 10.3945/ajcn.113.072785.

- [39] Diogenes ME, Bezerra FF, Rezende EP, Taveira MF, Pinhal I, Donangelo CM. Effect of calcium plus vitamin D supplementation during pregnancy in Brazilian adolescent mothers: a randomized, placebo-controlled trial. Am J Clin Nutr 2013;98:82–91. https://doi.org/10.3945/ajcn.112.056275.
- [40] Jelsma JG, van Poppel MN, Galjaard S, Desoye G, Corcoy R, Devlieger R, et al. DALI: vitamin D and lifestyle intervention for gestational diabetes mellitus (GDM) prevention: an European multicentre, randomised trial – study protocol. BMC Pregnancy Childbirth 2013;13:142. https://doi.org/10.1186/1471-2393-13-142.
- [41] Naghshineh E, Sheikhaliyan S. Effect of vitamin D supplementation in the reduce risk of preeclampsia in nulliparous women. Adv Biomed Res 2016;5:7. https://doi.org/10.4103/2277-9175.175239.
- [42] Roth DE, Al Mahmud A, Raqib R, Akhtar E, Perumal N, Pezzack B, et al. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: the AViDD trial. Nutr J 2013;12:47. https://doi.org/10.1186/1475-2891-12-47.
- [43] Asemi Z, Tabassi Z, Heidarzadeh Z, Khorammian H, Sabihi SS, Samimi M. Effect of calcium-vitamin D supplementation on metabolic profiles in pregnant women at risk for pre-eclampsia: a randomized placebo-controlled trial. Pak J Biol Sci 2012;15:316–24.
- [44] Taherian AA, Taherian A, Shirvani A. Prevention of preeclampsia with lowdose aspirin or calcium supplementation. Arch Iran Med 2002;5:151–6.
- [45] Marya RK, Rathee S, Marrow M. Effect of calcium and vitamin D supplementation on toxaemia of pregnancy. Gynecol Obstet Investig 1987;24: 38–42.
- [46] Delvin EE, Salle BL, Glorieux FH, Adeleine P, David LS. Vitamin D supplementation during pregnancy: effect on neonatal calcium homeostasis. J Pediatr 1986;109:328–34.
- [47] Mallet E, Gügi B, Brunelle P, Hénocq A, Basuyau JP, Lemeur H. Vitamin D supplementation in pregnancy: a controlled trial of two methods. Obstet Gynecol 1998;68:300–4.
- [48] Brooke OG, Brown IR, Bone CD, Carter ND, Cleeve HJ, Maxwell JD, et al. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. Br Med J 1980;280:751–4.
- [49] Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundgvist C, Cifkova R, De Bonis M, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J 2018;39:3165–241. https://doi.org/10.1093/eurheartj/ehy340.
- [50] Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:1545–88. https://doi.org/10.1161/01.str.0000442009.06663.48.
- [51] ACOG Practice Bulletin No. 202: Gestational hypertension and preeclampsia. Obstet Gynecol 2019 Jan;133:e1-25. https://doi.org/10.1097/ AOG.00000000000003018.

- [52] Cicero AF, Degli Esposti D, Immordino V, Morbini M, Baronio C, Rosticci M, et al. Independent determinants of maternal and fetal outcomes in a sample of pregnant outpatients with normal blood pressure, chronic hypertension, gestational hypertension, and preeclampsia. J Clin Hypertens 2015;17: 777–82. https://doi.org/10.1111/jch.12614.
- [53] Borghi C, Cicero AF, Degli Esposti D, Immordino V, Bacchelli S, Rizzo N, et al. Hemodynamic and neurohumoral profile in patients with different types of hypertension in pregnancy. Intern Emerg Med 2011;6:227–34. https:// doi.org/10.1007/s11739-010-0483-5.
- [54] Khaing W, Vallibhakara SA, Tantrakul V, Vallibhakara O, Rattanasiri S, McEvoy M, et al. Calcium and vitamin D supplementation for prevention of preeclampsia: a systematic review and network meta-analysis. Nutrients 2017;9. https://doi.org/10.3390/nu9101141. pii: E1141.
- [55] Bujold E, Hyett J. Calcium supplementation for prevention of pre-eclampsia. Lancet 2019 Jan 26;393:298–300. https://doi.org/10.1016/S0140-6736(18) 32161-5.
- [56] Reid IR, Birstow SM, Bolland MJ. Calcium and cardiovascular disease. Endocrinol Metab 2017;32:339–49. https://doi.org/10.3803/EnM.2017.32.3.339.
- [57] WHO recommendation: Calcium supplementation during pregnancy for the prevention of pre-eclampsia and its complications. Geneva: World Health Organization; 2018.
- [58] Cardús A, Parisi E, Gallego C, Aldea M, Fernández E, Valdivielso JM. 1,25-Dihydroxyvitamin D3 stimulates vascular smooth muscle cell proliferation through a VEGF-mediated pathway. Kidney Int 2006;69:1377–84.
- [59] Evans KN, Bulmer JN, Kilby MD, Hewison M. Vitamin D and placental-decidual function. J Soc Gynecol Investig 2004;11:263–71.
- [60] Dinca M, Serban MC, Sahebkar A, Mikhailidis DP, Toth PP, Martin SS, et al. Does vitamin D supplementation alter plasma adipokines concentrations? A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2016;107:360-71.
- [61] Pilz S, Zittermann A, Trummer C, Theiler-Schwetz V, Lerchbaum E, Keppel MH, et al. Vitamin D testing and treatment: a narrative review of current evidence. Endocr Connect 2019;8:R27–43. https://doi.org/10.1530/EC-18-0432.
- [62] Faridi KF, Lupton JR, Martin SS, Banach M, Quispe R, Kulkarni K, et al. Vitamin D deficiency and non-lipid biomarkers of cardiovascular risk. Arch Med Sci 2017;13:732-7. https://doi.org/10.5114/aoms.2017.68237.
- [63] Holick MF. The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord 2017;18:153–65. https://doi.org/10.1007/s11154-017-9424-1.
- [64] Mazidi M, Michos ED, Banach M. The association of telomere length and serum 25-hydroxyvitamin D levels in US adults: the National Health and Nutrition Examination Survey. Arch Med Sci 2017;13:61–5. https://doi.org/ 10.5114/aoms.2017.64714.
- [65] Karras SN, Wagner CL, Castracane VD. Understanding vitamin D metabolism in pregnancy: from physiology to pathophysiology and clinical outcomes. Metabolism 2018;86:112–23. https://doi.org/10.1016/j.metabol.2017.10.001.