

Vitamin D and miscarriage

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Vitamin D and miscarriage: a systematic review and meta-analysis

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Objective: To investigate whether a significant association between vitamin D status and the risk of miscarriage or recurrent miscarriage (RM) exists.

Design: Systematic review and meta-analysis.

Setting: Not applicable.

Patient(s): Women with miscarriage and RM.

Intervention(s): We searched the Ovid MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature, and Cochrane Central Register of Controlled Trials from database inception to May 2021. Randomized and observational studies investigating the association between maternal vitamin D status and miscarriage and/or vitamin D treatment and miscarriage were included.

Main Outcome Measure(s): The primary outcome was miscarriage or RM, with vitamin D status used as the predictor of risk. Whether vitamin D treatment reduces the risk of miscarriage and RM was also assessed.

Result(s): Of 902 studies identified, 10 (n = 7,663 women) were included: 4 randomized controlled trials (n = 666 women) and 6 observational studies (n = 6,997 women). Women diagnosed with vitamin D deficiency (<50 nmol/L) had an increased risk of miscarriage compared with women who were vitamin D replete (>75 nmol/L) (odds ratio, 1.94; 95% confidence interval, 1.25–3.02; 4 studies; n = 3,674; I² = 18%). Combined analysis, including women who were vitamin D insufficient (50–75 nmol/L) and deficient (<50 nmol/L) compared with women who were replete (>75 nmol/L), found an association with miscarriage (odds ratio, 1.60; 95% confidence interval, 1.11–2.30; 6 studies; n = 6,338; I² = 35%). Although 4 randomized controlled trials assessed the effect of vitamin D treatment on miscarriage, study heterogeneity, data quality, and reporting bias precluded direct comparison and meta-analysis. The overall study quality was “low” or “very low” using the Grading of Recommendations, Assessment, Development and Evaluations approach.

Conclusion(s): Vitamin D deficiency and insufficiency are associated with miscarriage. Whether preconception treatment of vitamin D deficiency protects against pregnancy loss in women at risk of miscarriage remains unknown.

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El resumen está disponible en Español al final del artículo.

Key Words: Vitamin D, miscarriage, recurrent miscarriage



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Miscarriage causes significant physical and psychological harm, complicating 15.3% of recognized pregnancies. Globally, 10.8%, 1.9%, and 0.7% of women experience 1, 2, and 3 miscarriages, respectively (1). Importantly, a woman's risk of recurrent miscarriage (RM; ≥ 2 losses) increases by 10% for each additional loss, up to 42% for women with ≥ 3 losses (1, 2). The risk of other major obstetric and psychological complications, including preterm birth, pre-eclampsia, stillbirth, depression, and

posttraumatic stress, also increases for women experiencing RM (2). Preconception investigation and management are at the forefront of research efforts to reduce the risk of pregnancy loss.

Vitamin D deficiency (low serum levels of 25-hydroxyvitamin D (25(OH)D)) is a major global health concern, with pregnant women and those planning pregnancy at increased risk (3–5). Although traditionally associated with maternal and newborn bone disease, vitamin D deficiency is more prevalent in women who develop major reproductive and obstetric complications, including preeclampsia, gestational diabetes, and preterm birth (6–9).

Vitamin D supplementation is a safe and well-tolerated treatment (4, 7). Furthermore, meta-analyses have shown that low-dose antenatal vitamin D supplementation (22 trials, 3,725 women) reduces preeclampsia (risk ratio [RR], 0.48; 95% confidence interval [CI], 0.30–0.79), gestational diabetes (RR, 0.51; 95% CI, 0.27–0.97), and low neonatal birth weight (RR, 0.55; 95% CI, 0.35–0.87) (7). For women with subfertility, the chance of live birth with assisted reproductive technology appears significantly higher if vitamin D replete (odds ratio [OR], 1.33; 95% CI, 1.08–1.65) (6); however, association data has been highly heterogenic, with the results of the “supplementation of vitamin D and reproductive outcome” prospective, multicenter, interventional randomized controlled trial (RCT) much anticipated (6, 10–13).

The plausibility of a role for vitamin D in pregnancy and miscarriage is supported by the expression of the vitamin D-activating enzyme *CYP27B1* in maternal decidua and fetal trophoblast early in pregnancy (14). In previous studies, we have shown that the human placenta is a key tissue for the accumulation of both 25(OH)D and active 1,25-dihydroxyvitamin D (1,25(OH)₂D) (15), with the potential to exert important effects on trophoblast invasion, placental spiral artery remodeling, and immune cell function (16–18). These processes are impaired in human miscarriage, with aberrant endometrial receptivity and dysregulated placentation identified early after initial conception (19–23). It is, therefore, possible that a low serum 25(OH)D level contributes to miscarriage pathophysiology via a concomitant decrease in placental 1,25(OH)₂D and resultant placental dysregulation. However, whether vitamin D deficiency is more prevalent in women with miscarriage and RM remains unclear, with early pregnancy association data largely excluded from former meta-analyses.

The primary aim of this systematic review and meta-analysis was to evaluate the association between vitamin D status and pregnancy loss, including spontaneous miscarriage and RM. We also systematically evaluated whether vitamin D treatment reduces the risk of miscarriage. Whether the timing of vitamin D assessment and treatment or vitamin D dose influences miscarriage risk was also of interest.

MATERIALS AND METHODS

This is a protocol-driven systematic review and meta-analysis, prospectively registered with the International Prospective Register of Systematic Reviews (CRD42021259899) with the results reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines

(24). All data were obtained from previously published studies; therefore, institutional review board approval was not obtained. We searched the Embase (1974 to May 2021), MEDLINE (1946 to May 2021), Cochrane Central Register of Controlled Trials (inception to May 2021), and the Cumulative Index to Nursing and Allied Health Literature (inception to May 2021) databases. The MEDLINE search is detailed in [Supplemental Appendix 1](#) (available online); search terms and functions were amended for each database. No language restrictions were applied.

All abstracts retrieved were independently reviewed by 2 reviewers (A.d.M., E.J.M.), and decision regarding full-text retrieval arbitrated by a third reviewer (J.A.T.). Full texts were reviewed (A.d.M., E.J.M.) and discussed as a group (J.A.T., N.S.P.P.N., A.d.M., E.J.M.) regarding inclusion eligibility. Reference lists were searched for additional articles. Conference abstracts and prospective trial registries were searched for relevant items.

Study Selection

Predefined eligibility criteria were developed to answer 2 major questions: is vitamin D deficiency associated with an increased risk of subsequent miscarriage or RM, and does vitamin D treatment reduce the risk of miscarriage or RM?

Studies were included if the criteria for either question met the predefined patient/population, intervention, comparison and outcomes criteria ([Supplemental Fig. 1](#), available online). Observational and randomized studies were eligible. Animal studies, case reports, case series, abstracts, letters, and review articles were excluded. Women receiving any form of fertility treatment were excluded because they were considered a distinct study population with an increased miscarriage risk, the reasons for which appear multifactorial (25–29). Vitamin D serum assessment, using the 25(OH)D levels, was initially confined to preconception or the first trimester; however, this was revised to include early second trimester because several studies investigated the study question but included women with vitamin D assessment shortly after the first trimester, that is, at the 14-week booking appointment. Although 1 study performed preconception vitamin D assessment, for this analysis (raw data provided by investigators), association analysis was performed using the first trimester vitamin D levels (30). Studies measuring the levels of 1,25(OH)₂D or other vitamin D metabolites without inclusion of 25(OH)D were excluded. For the association studies, the control group may have included pregnant women who experienced other adverse pregnancy outcomes.

Outcome and Exposure

As per the Endocrine Society guidance, vitamin D deficiency, insufficiency, and replete were defined as 25(OH)D levels of <50, 50–75, and >75 nmol/L, respectively, with the assay method details recorded (4).

The primary outcome measure was miscarriage, including the first (≤ 12 weeks) and second (<24 weeks) trimester losses. The clinical pregnancy (preconception studies) and live birth rates were recorded where reported.

Data Extraction

Data were extracted by 3 reviewers independently (A.d.M., E.J.M., N.S.P.P.N.) using a standardized pro forma data collection. Discrepancies were arbitrated by a fourth reviewer (J.A.T.). Study characteristics, methodology, and outcomes were recorded and summarized.

Quality Assessment

Quality assessment was performed by 3 reviewers independently (A.d.M., E.J.M., N.S.P.P.N.). Discrepancies were evaluated by a fourth reviewer (J.A.T.). Randomized controlled trials were assessed using the Cochrane risk-of-bias tool for randomized trials (RoB2) (31). Cohort and case-control observational studies were assessed using the Newcastle-Ottawa Scale (NOS) score for meta-analysis of nonrandomized studies (32). Consistent with prior published systematic reviews (33–35), a modified NOS tool (33) was used for cross-sectional study (36) quality assessment. The reliability of study findings and risk of bias due to methodology, data quality, and study heterogeneity and more broadly the interpretation of the study's findings were assessed.

We also employed the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach (37) to evaluate the confidence in available evidence for each intervention and aid translation into clinical practice. Two independent reviewers (N.S.P.P.N., A.d.M.) assessed the certainty of the evidence for the following domains: risk of bias in the primary studies for each intervention; inconsistency across the included trials; and indirectness or imprecision in the pooled effect estimates. We modified this approach to use the same principles to evaluate the quality of evidence for observational studies in each relevant population. A final overall assessment was made for each intervention as high, moderate, low, or very low in consultation with a third reviewer (J.A.T.).

Data Analysis

Dichotomous outcome data were assessed according to vitamin D status (4), with 2×2 tables constructed to calculate the ORs and 95% CIs. The Mantel-Haenszel method random-effects models were used for meta-analysis. Summary ORs were plotted using forest plots, which were visually inspected, and heterogeneity quantitatively assessed using I^2 (38). No zero-cell adjustments were required. When published texts did not report data for the 2×2 table analysis, the investigators were contacted. Review Manager 5.4 (RevMan) was used for data analysis (39). The primary analysis included all studies that measured vitamin D status before the potential event of miscarriage. Sensitivity analysis was conducted for association studies to examine only those of high quality (NOS/modified NOS score of 8 or 9). Meta-regression was not undertaken due to a paucity of studies. Funnel plots were not analyzed due to the limited number of studies; however, this was considered qualitatively.

RESULTS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the review process is

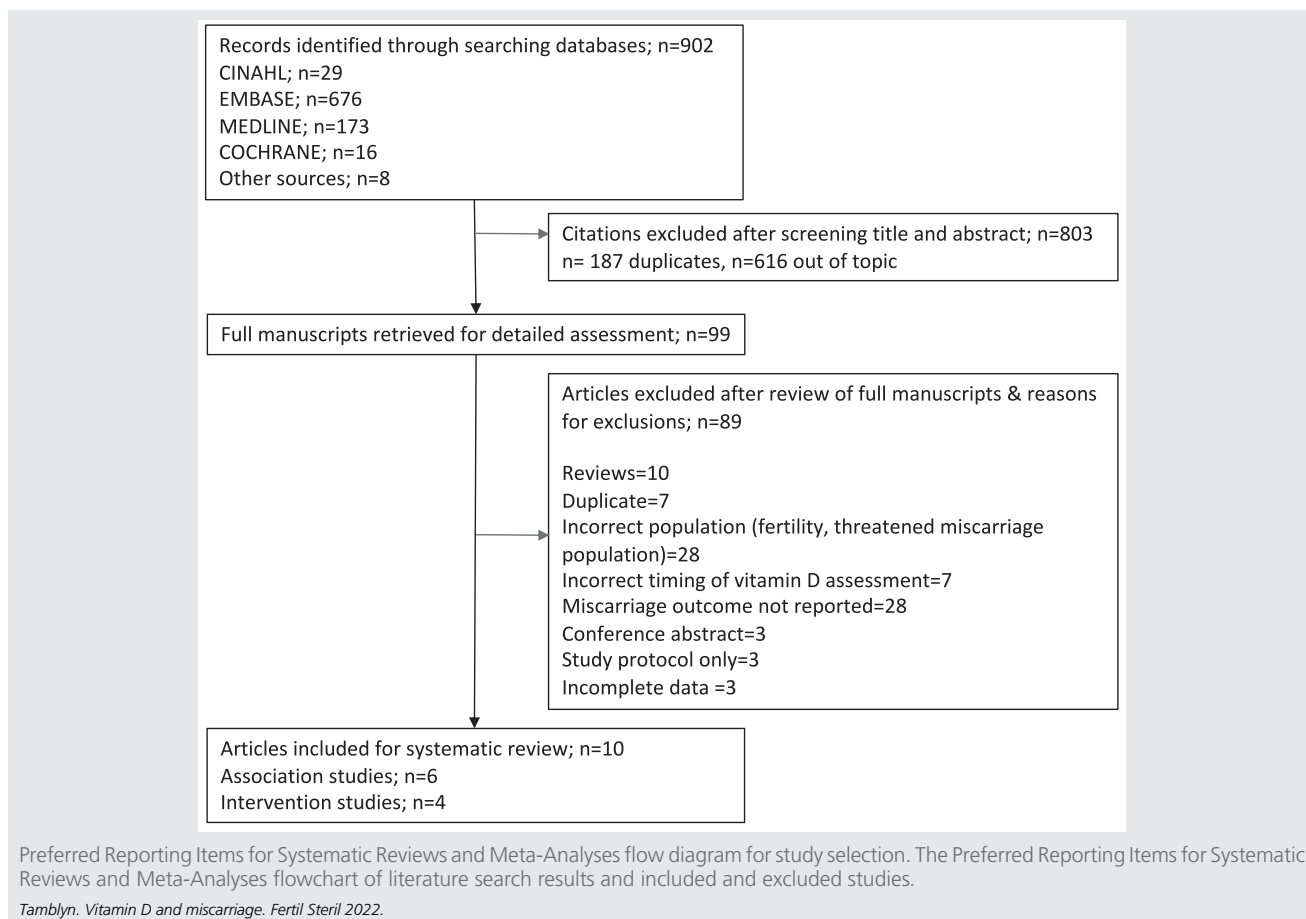
illustrated in Figure 1. The search yielded 894 citations and a further 8 identified from other sources. Of these, 803 were excluded ($n = 187$ duplicates, $n = 616$ out of topic) because it was clear from the title and abstracts that they did not fulfill the selection criteria. Full manuscripts were obtained for 99 studies, with a total of 89 excluded, 10 reviews, 7 unrecognized duplicates, 28 studies with incorrect study population, 7 studies that did not assess the first or early second trimester vitamin D status, 28 studies that did not report miscarriage as outcome, 3 conference abstracts, 3 study protocols, and 3 studies that included incomplete data (5 investigators directly contacted (30, 40–43) 3 provided additional data and were included (30, 40, 43)). Overall, 10 studies ($n = 7,663$) met the original inclusion criteria: 4 interventional studies ($n = 666$) investigating vitamin D treatment and miscarriage prevention and 6 observational studies ($n = 6,997$) investigating the association between maternal vitamin D status and pregnancy outcomes, including miscarriage. A detailed summary of the included study characteristics is shown in Table 1 (30, 36, 40, 43–45) and Supplemental Table 1 (available online).

Is Vitamin D Deficiency Associated with Miscarriage or RM?

Study overview. Overall, 6 observational studies assessed the association between vitamin D status and miscarriage (30, 36, 40, 43–45). This included 1 cross-sectional study, and the remainder were cohort studies. Prospective recruitment occurred in 3 (30, 40, 43), the remaining studies were retrospective. Study population size was variable, with the smallest involving 235 women (44) and largest involving 2,073 women (43). For most, recruitment was exclusively in the first trimester with low- and high-risk women included with no exclusions on the basis of medical or obstetric history. Flood-Nichols et al. (44) excluded women with chronic medical conditions, infertility treatment, and pregnancy loss after the first trimester, and Thiele et al. (45) excluded women who did not meet the eligibility criteria for out-of-hospital midwife-led care. The remaining studies did not exclude women on the basis of a history of previous miscarriage; thus, the study population will have included women with RM as well as those without, and a separate subgroup analysis of the first loss and recurrent loss groups is not possible. Thiele et al. (45) completed the 25(OH)D levels at initial appointment (mean, 13.2/40 [SD, 6.7 weeks]) (45). Only the study by Mumford et al. (30) specifically investigated women with a history of miscarriage (1–2 losses).

Considering the classification of vitamin D deficiency, 3 studies (40, 43, 44) used strata consistent with the Endocrine Society recommendations: deficient, <50 nmol/L; insufficient, 50–75 nmol/L; and sufficient, >75 nmol/L (4, 9). Flood-Nichols et al. (44) subclassified vitamin D deficiency into severe (<25 nmol/L) and moderate (25–50 nmol/L) (44). Thiele et al. (45) used similar cutoffs with deficiency <20.9 ng/mL equivalent to <52.3 nmol/L, insufficiency 21–29.9 ng/mL and sufficient >30 ng/mL equivalent to >75 nmol/L (45). Mumford et al. (30) simply classified women as vitamin D insufficient (<75 nmol/L) or sufficient (>75 nmol/L) (30).

FIGURE 1



Christoph et al. (36) used an alternative classification: severe, <25 nmol/L; mild, 25–50 nmol/L; and sufficient >50 nmol/L (36), limiting some analysis. The timing of vitamin D assessment was relatively consistent and at the point of study recruitment. Only the study by Mumford et al. (30) assessed vitamin D status before conception and at 8 weeks.

Overall, miscarriage diagnosis was inconsistently reported; 2 prospective studies (30, 40) used ultrasound \pm human chorionic gonadotropin, and 1 used patient-reported data (43). All retrospective studies used electronic patient records (30, 44, 45) with no method specified. Miscarriage definitions were also heterogenic (30, 36, 40, 43, 45), including the first and second trimester losses to 23 weeks, loss from 10–20 weeks, and the first trimester loss only (44).

Quality assessment. Overall, 6 observational studies were all of very high quality (NOS score of 8 or 9). As summarized in Supplemental Table 2 (available online), studies were primarily deducted points due to loss to follow-up (30, 36, 44). The GRADE approach (37) was used to assess the overall quality of the evidence. The overall quality for the association between miscarriage and vitamin D deficiency (and insufficiency) was very low (Supplemental Table 3, available online).

Data analysis. A meta-analysis comparing vitamin D-deficient (<50 nmol/L) women with vitamin D-replete (>75 nmol/L) women found a statistically significantly increased miscarriage risk (OR, 1.94; 95% CI, 1.25–3.02; 4 studies; $n = 3,674$; $I^2 = 18\%$) (Fig. 2). A combined analysis comparing vitamin D-deficient or vitamin D-insufficient (50–75 nmol/L) women with vitamin D-replete women similarly found a statistically significantly increased miscarriage risk (OR, 1.60; 95% CI, 1.11–2.30; 6 studies; $n = 6,338$; $I^2 = 35\%$) (Fig. 3).

Planned sensitivity analysis, including only those studies determined at lowest risk of bias (NOS score of 8 or 9), was not performed because all studies were assessed to be of very high quality. There was no evidence to suggest bias from lower-quality studies for either the meta-analysis assessing the risk of miscarriage in women with deficient and sufficient levels of vitamin D or the combined meta-analysis comparing the risk of miscarriage in women with deficient and insufficient levels compared with women with sufficient levels of vitamin D.

Planned subgroup analysis for preconception vitamin D assessment and RM identified 1 eligible study. In this prospective cohort, sufficient preconception 25(OH)D levels were associated with a statistically significant increase in clinical

TABLE 1

Summary of observational study characteristics: a summary of the study characteristics of all included observational studies examining the association between vitamin D status and miscarriage

Author (year)	Country	Study design	Recruitment period	Study population	GA at recruitment	Recurrent miscarriage	Inclusion criteria	Exclusion criteria	Timing of vitamin D measurement	Definition of vitamin D deficiency	Serum vitamin D measurement	Study population vitamin D status	Miscarriage definition	Miscarriage outcome measurement	Summary of results	Outcome for the nonevent group
Andersen (2015) (40)	Denmark	Prospective cohort	January 2010 to December 2012	1,684 pregnant women, Odense Child Cohort study	First and second trimester	No	Low- and high-risk pregnant women	All inclusive	First or second trimester	25(OH)D Deficient, <50 nmol/L; insufficient, 50–75 nmol/L; sufficient, >75 nmol/L	LC-MS (Thermo Scientific TLX1 system) 25(OH)D2 and 25(OH)D3. C3 epimer not distinguished. Lowest detectable level, 0.15 nmol. External calibration.	No miscarriage group (n = 1,625); median 25(OH)D nmol/L, 66.0 (IQR, 50.37–80). Miscarriage group at (n = 58); median 25(OH)D nmol/L, 55.6 (IQR, 43.60–69.92)	Missed, complete or incomplete miscarriage, or blighted ovum	TV USS	Miscarriage rate: women with vitamin D deficiency, 21/417; women with vitamin D insufficiency, 29/713; women with vitamin D sufficiency, 8/553	Pregnant women who did not experience miscarriage
Bärebring (2018) (43)	Sweden	Prospective cohort	Autumn 2013 (September to November) to Spring 2014 (February to June)	2,073 pregnant women, GRAVID study, cohort study	4–16 wk	No	Low- and high-risk pregnant women	Termination of pregnancies, multiple pregnancy	First trimester	25(OH)D Deficient, <50 nmol/L; insufficient, 50–75 nmol/L; sufficient, >75 nmol/L	LC-MS/MS (API 4000). Measuring range, 6–450 nmol/L for 25(OH)D3 and 6–225 nmol/L 25(OH)D2. Interassay CV 6% at 40 nmol/L of 25(OH)D3 and 25(OH)D2.	25(OH)D replete, n = 690 (35.1%); 25(OH)D insufficient, n = 788 (40.1%); 25(OH)D deficient, n = 489 (24.8%)	nPregnancy loss at <22 wk of GA	Self-reported	Miscarriage rate: in women with vitamin D deficiency, 30/519; women with vitamin D insufficiency, 37/828; women with vitamin D sufficiency, 30/726	Pregnant women who did not experience miscarriage
Christoph (2020) (36)	Switzerland	Retrospective cross-sectional	2012–2015	1,382 pregnant women, University Hospital Bern, Inselspital	First and second trimester	No	Low- and high-risk pregnant women	All inclusive	First or second trimester	25(OH)D Severely deficient, <25 nmol/L; mildly deficient, 25–49 nmol/L; sufficient, >50 nmol/L	CLIA (LIAISON XL, DiaSorin). DiaSorin 25OH vitamin D total control set. External quality control quarterly, Swiss Center for Quality Control.	25(OH)D ≥ 50 nmol/L, n = 370 (26.8%); 25(OH)D <50 nmol/L, n = 1,012 (73.2%)	Pregnancy loss at <20 wk of GA and/or extraction of an embryo or fetus ≤500 g	Electronic health care records	Miscarriage rate: women with vitamin D deficiency, 39/1,012; women with vitamin D sufficiency, 7/370	Pregnant women who did not experience miscarriage but may have experienced other adverse pregnancy outcomes
Flood-Nichols (2015) (44)	United States	Retrospective cohort	Not reported	310 pregnant women, tertiary military medical center, Washington	8–12 wk	No	Low-risk nulliparous pregnant women (≥ 18 y)	Women with an increased risk of vitamin D deficiency (anticonvulsants, renal and cardiovascular diseases, and preexisting diabetes mellitus) or prior fetal loss before the first trimester	First trimester	25(OH)D Severely deficient, <25 nmol/L; deficient, <50 nmol/L; insufficient, 51–74 nmol/L; sufficient, >75 nmol/L	ELISA (Diazyme) assay. Interassay variability, 9.3%; intra-assay variability, 7.8%. LC-MS comparative analysis correlation coefficient, 0.95 (–8.23% bias).	25(OH)D replete, n = 70 (29.8%); 25(OH)D insufficient, n = 141 (60.0%); 25(OH)D deficient, 10.2%	nSpontaneous pregnancy loss at ≤12 wk	Electronic health care records	Miscarriage rate: women with vitamin D deficiency, 2/20; women with vitamin D insufficiency, 10/115; women with vitamin D sufficiency, 4/57	Pregnant women who did not experience miscarriage but may have experienced other adverse pregnancy outcomes
Mumford (2018) (30)	United States	Prospective cohort	2007–2011	1,191 women with a history of recurrent pregnancy loss, EAGeR Trial (4 medical sites)	Preconception	Yes	Preconception women attempting pregnancy (8–40 y) with 1–2 prior pregnancy losses, recruited at 4 clinical sites	Prior infertility treatment, pelvic inflammatory disease, tubal occlusion, endometriosis, anovulatory disorder, polycystic ovary syndrome, or uterine abnormality	Preconception	25(OH)D Insufficient, <75 nmol/L; sufficient, ≥75 nmol/L	ELISA (BioVendor R&D) for D2 and D3. Interassay CV 15.8% and 13.1%. Lower limit of detection, 4.0 nmol/L.	25(OH)D replete, n = 555 (47%); 25(OH)D insufficient/deficient (<75 nmol/L), n = 636 (53%)	Pregnancy loss at ≤23 wk after positive urine hCG pregnancy test (including home test) or USS confirmation	Urine hCG after and/or USS	Miscarriage rate: women with vitamin D insufficiency, 97/382; women with vitamin D sufficiency, 88/392	Women who had a biochemical pregnancy and did not experience a miscarriage

TABLE 1

Continued.

Author (year)	Country	Study design	Recruitment period	Study population	GA at recruitment	Recurrent miscarriage	Inclusion criteria	Exclusion criteria	Timing of vitamin D measurement	Definition of vitamin D deficiency	Serum vitamin D measurement	Study population vitamin D status	Miscarriage definition	Miscarriage outcome measurement	Summary of results	Outcome for the nonevent group
Thiele (2019) (45)	United States	Retrospective cohort	2009–2013	357 pregnant women registered at 2 midwife-led birth practices in Portland and Seattle	<36 wk	No	Low- and high-risk pregnant women	Underlying calcium or vitamin D metabolic disorder	<36 wk of GA 13.24 ± 6.65 wk	25(OH)D ng/mL (52.3 nmol/L); Deficient, <20.9 ng/mL; insufficient, >21.0 and <29.9 ng/mL; sufficient, >30 ng/mL (75 nmol/L)	Not reported	25(OH)D replete, n = 148 (47%); 25(OH)D insufficient/deficient, n = 167 (53%)	nSpontaneous abortion at <20 wk of GA	Electronic records	Miscarriage rate: women with vitamin D deficiency or insufficiency, 10/198; women with vitamin D sufficiency, 3/159	Pregnant women who did not experience miscarriage but may have experienced other adverse pregnancy outcomes

Note: CLIA = chemiluminescent immunoassay; CV = coefficient of variation; EAGEr = Effects of Aspirin in Gestation and Reproduction; ELISA = enzyme-linked immunosorbent assay; hCG = human chorionic gonadotropin; GA = gestational age; IQR = interquartile range; LC-MS = liquid chromatography-tandem mass spectrometry; LC-MS/MS = tandem liquid chromatography-tandem mass spectrometry; TV = transvaginal; USS = ultrasound; 25(OH)D = 25-hydroxyvitamin D.

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pregnancy compared with insufficient levels (adjusted RR, 1.10; 95% CI, 1.01–1.20; n = 1,191). Higher preconception 25(OH)D levels were associated with a reduced risk of pregnancy loss (RR, 0.88; 95% CI, 0.77–0.99). At 8 weeks, a statistically significant reduction was not observed (adjusted RR, 0.98; 95% CI, 0.95–1.01).

Does Vitamin D Treatment Reduce the Risk of Miscarriage or RM?

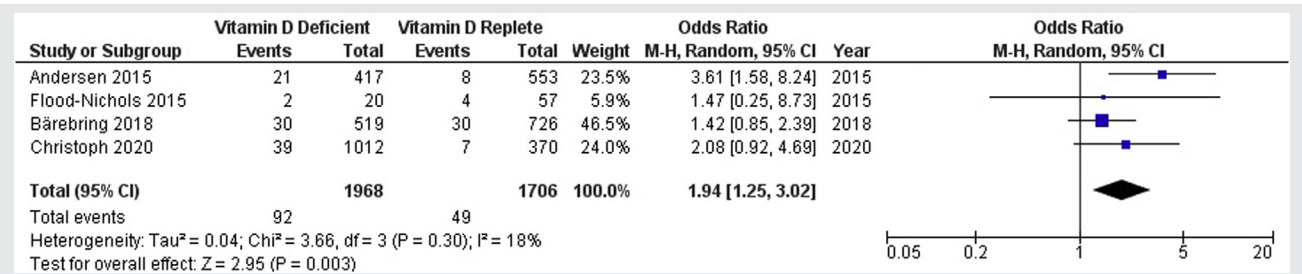
Study overview. Overall, 4 RCT studies met the initial inclusion criteria (46–49), with a systematic assessment detailed for reference (Supplemental Table 1). Overall, the sample sizes were small (n = <100), except that in the study by Hollis et al. (46) (n = 502). In 3 RCTs, the population of interest was high-risk women with a history of RM either planning pregnancy (47, 48) or pregnant in the first trimester (49). Conversely, Hollis et al. (46) included low-risk pregnant women with no history of RM.

Interventions were highly heterogenic, preventing direct comparative analysis. In 2 RCTs that assessed preconception vitamin D treatment, the regimes used were highly disparate (47, 48). In the study by Rafiee et al. (47), women received 300,000 IU of intramuscular vitamin D3 or placebo, whereas in the study by Samimi et al. (48), women received 400 IU of oral vitamin D3 or placebo daily (duration unspecified). In the study by Rafiee et al. (47), women also received 3 courses of lymphocyte immunization therapy at 4-week intervals with barrier contraception recommended 3 months after treatment. In the study by Ibrahim et al. (49), the effects of alfacalcidol (1 α -hydroxyvitamin D3 prodrug, 0.25 μ g twice daily) was assessed with no placebo control; both groups also received folic acid 5 mg, aspirin 81 mg, and progesterone rectal suppositories 400 mg. Alfacalcidol, which is hydroxylated to active 1 α ,25(OH)₂D₂, is ordinarily reserved for patients with renal insufficiency and/or renal 1 α -hydroxylation impairment (50). In the study by Hollis et al. (46), 3 groups were compared with all women receiving 400 IU of vitamin D3 and either 0 (placebo), 1,600, or 3,600 IU of vitamin D3 from <16 weeks of gestation.

Miscarriage was reported as the primary outcome in 1 RCT (48). Rafiee et al. (47) and Ibrahim et al. (49) reported before treatment and after treatment changes in immune cell marker levels (interferon γ , T helper 17, and T regulatory cell levels/ratios), with continuing pregnancy (>14 weeks), miscarriage (49), and clinical pregnancy outcome (47) as the secondary measures. In the study by Hollis et al. (46), miscarriage and live birth were secondary outcome measures, with maternal and neonatal vitamin D status at delivery of primary interest (46). The first trimester outcome data, including miscarriage, were not obtained.

Quality assessment. The included studies were of highly variable quality; 3 RCTs were at high risk of bias (46, 47, 49), and 1 was at low risk of bias (48) (Supplemental Fig. 2, available online). Three RCTs failed to provide a prospectively published trial protocol (46, 47, 49). Hollis et al. (46) reported significant loss to follow-up (almost one third of participants), and a high risk of attrition bias (46). In the study by Ibrahim et al. (49), there was no placebo-control or assessor blinding.

FIGURE 2



Comparison of the risk of miscarriage by vitamin D deficient and sufficient status. Forest plot summarizing the results of the meta-analysis comparing the risk of miscarriage in women with deficient and sufficient levels of vitamin D. CI = confidence interval; M-H = Mantel-Haenszel.

Tamblin. *Vitamin D and miscarriage. Fertil Steril* 2022.

There were significant concerns regarding reporting bias in the study by Rafiee et al. (47), which was excluded from further data analysis. Specifically, the miscarriage rates were reported for controls (6/22) but not cases (×/22) (47). It is possible that no miscarriage events were recorded; however, this was unclear from the published findings (the investigators were contacted before exclusion). The GRADE approach was used to summarize the quality of the evidence, and this was considered low or very low (Supplemental Table 4, available online) (37).

Data analysis. Due to the study heterogeneity and concerns over data quality and reporting bias, direct comparison and meta-analysis were precluded. A detailed descriptive summary is presented in Supplemental Table 1.

The study by Samimi et al. (48), which was at low risk of bias, reported significantly higher miscarriage rates in controls (n = 13/38, 34.2%) than in women with RM who conceived after vitamin D treatment (n = 5/39, 12.8%; P = .03; OR, 3.53; 95% CI, 1.12–11.2). After adjustment for age, gravidity, previous miscarriages, and interleukin-23, no significant association (OR, 0.37; 95% CI, 0.06–2.26) was measured (48).

Hollis et al. (46) found no statistically significant difference in the miscarriage rates between the control and

treatment (combined) groups (n = 8/166 [4.8%], 400 IU; n = 5/167 [3.0%], 2,000 IU; n = 10/169 [6.0%], 4,000 IU). In our analysis that combined the treatment groups and compared them with the 400-IU group, no statistically significant difference was observed (OR, 0.92; 95% CI, 0.38–2.22) (46).

In the study by Ibrahim et al. (49), although fewer women with RM experienced miscarriage after vitamin D treatment (6/20, 30.0%) than controls (9/20, 45.0%), the difference was not statistically significant (P = .5).

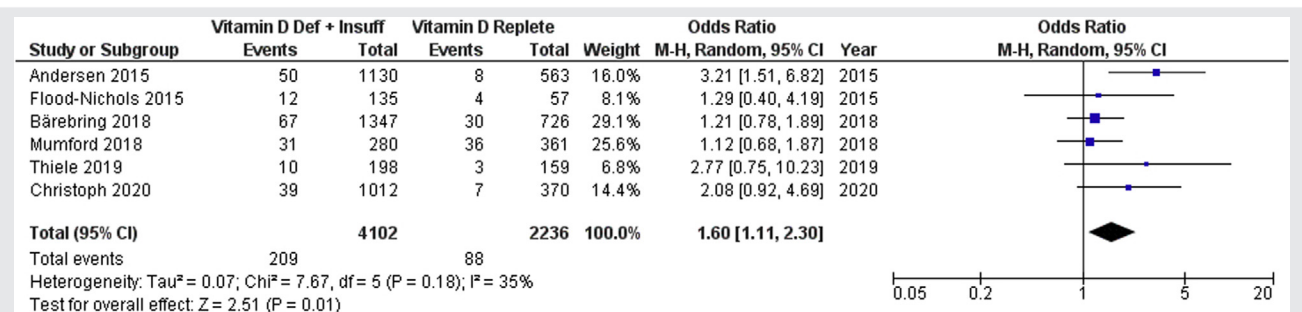
DISCUSSION

Summary of Main Findings

Women who were vitamin D deficient were at significantly increased risk of miscarriage compared with those who were vitamin D replete. This association was maintained when women with insufficient levels were included, with a biologic gradient evident. Overall, the NOS quality of association studies was high, whereas the modified GRADE assessment of the quality of evidence was very low.

Because only 1 association study recruited women with RM, preconception subgroup meta-analysis was precluded. From this data, sufficient preconception 25(OH)D was

FIGURE 3



Comparison of the risk of miscarriage by vitamin D deficient + insufficient and sufficient status. Forest plot summarizing the results of the meta-analysis comparing the risk of miscarriage in women with deficient and insufficient levels of vitamin D combined and women with sufficient levels of vitamin D. CI = confidence interval; M-H = Mantel-Haenszel.

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associated with a significant increased chance of live birth and clinical pregnancy and lower risk of pregnancy loss. Because an association was not observed when vitamin D assessment was delayed until 8 weeks (30), preconception vitamin D status appears important.

Our review found insufficient evidence to accurately assess whether vitamin D treatment reduces the risk of spontaneous miscarriage or RM. The RCTs identified, although inclusive of women with RM, were confounded by a small sample size, varying interventional regimes and high risk of bias. Most larger vitamin D RCTs did not include miscarriage as an outcome, with pregnant women at low risk of RM and often not vitamin D deficient included. The 1 RCT identified as low risk of bias suggested a positive effect of preconception vitamin D for women with RM (48).

Interpretation

The presence of key vitamin D metabolic enzymes and the vitamin D receptor (VDR) in the endometrium (51) and first trimester placenta (14) suggests a role for vitamin D before conception and/or in early pregnancy. This is further supported by the observation that women with higher endometrial expression of the VDR are more likely to become pregnant (51). Importantly, VDR function is closely linked to tissue levels of its ligand, the active form of vitamin D, 1,25(OH)₂D, which, in turn, is dependent on the synthesis of this metabolite from 25(OH)D by *CYP27B1*. The study described earlier did not report any statistically significant difference in endometrial *CYP27B1* in pregnant and nonpregnant women. However, the ability of *CYP27B1* to generate 1,25(OH)₂D locally within tissues is highly dependent on the availability of its substrate 25(OH)D (52). This so-called intracrine model for vitamin D function provides a mechanistic rationale for the link between vitamin D deficiency and adverse events in pregnancy, such as miscarriage, with low serum levels of 25(OH)D compromising endometrial or placental levels of 1,25(OH)₂D.

Vitamin D deficiency may also be increased in women with threatened miscarriage (53, 54); higher levels of deficiency (<75 nmol/L¹) (20/23, 87.0%) and lower mean 25(OH)D levels than those of pregnant controls (23.0 ± 56.4 vs. 25.0 ± 75.8 nmol/L, *P* = .008) were reported (54). Lower first trimester vitamin D levels were also reported in women with confirmed pregnancy loss (*n* = 30; 25(OH)D level, 86.1 nmol/L) than in pregnant controls (*n* = 30; 25(OH)D level, 123 nmol/L; *P* = .01). A positive association between low vitamin D level and pregnancy loss was reported (OR, 1.71; 95% CI, 1.2–2.4; *P* < .001). Vitamin D levels were also lower in nonpregnant women with ≥1 loss (*n* = 30; 30.7 ± 22.1 nmol/L; 95% CI, 22.5–38.9) than in nonpregnant women with prior successful birth (*n* = 30; 98.7 ± 22.0 nmol/L; 95% CI, 90.5–107.0) (53).

Strengths and Limitations

The strengths of our review stem from its pragmatic design and comprehensive search strategy, therefore providing the most up-to-date evidence on vitamin D and miscarriage. We employed standard methodology and assessed the risk of bias in included trials and observational studies following a prospectively registered protocol. Where appropriate, relevant subgroup analysis was performed, permitting a broader discussion of the evidence and critical appraisal of results to inform understanding of this important clinical question. We are confident that we identified all available studies, including contacting investigators for further data analysis and translating texts for accurate full review.

Our study adds to previous meta-analysis data (55), focusing specifically on early pregnancy vitamin D assessment and miscarriage. Although a nonsignificant summary RR for spontaneous abortion (*n* = 3 studies; summary RR, 1.04; 95% CI, 0.95–1.13) was previously identified, this likely reflects the sample size with only 3 eligible studies before 2017.

Still, our findings have several limitations, which primarily reflect the highly heterogeneous evidence identified and lack of interventional data for maternal vitamin D supplementation. For most studies, miscarriage was a secondary outcome and was insufficiently powered to assess the review question. The observational studies for which meta-analysis could be completed represent a diverse set of methodologies (from nested cohorts within an RCT to population level case-control studies in which controls also experienced the outcome) and populations (low- and high-risk women, with and without a history of miscarriage/RM). The existing evidence precluded the subgroup analysis of spontaneous miscarriage or RM populations, which is of certain clinical interest. Marked variations in miscarriage definition and assessment were also identified, with some studies only recruiting pregnant women from ≥10 to 12 weeks. Thiele et al. (45) used 25(OH)D data from the first booking appointments, which, albeit predominantly performed in early pregnancy, included all women who had their first appointment before 36 weeks. Because the miscarriage rates after a positive ultrasound result at 12 weeks are significantly lower (1), this datum is not representative of the broader population of women who experience miscarriage. It was also not possible to perform planned subgroup analyses for the first and second trimester miscarriages (reflecting that miscarriage was not the primary outcome). Because vitamin D exerts important early effects on endometrial invasion and trophoblast function, the inclusion of the second trimester loss is an important limitation. Because vitamin D may be anticipated less important for this group, this would introduce bias favoring the null hypothesis. Finally, methods to quantify vitamin D status are inherently inconsistent, with a range of different methods and accuracy ranges observed (56). Notably, 1 study failed to report the assessment method (45). Because vitamin D (25 [OH]D) assessment was routinely performed at the initial “early pregnancy” booking assessment in both clinical practices (Portland, OR, and Seattle, WA) between 2009 and 2013, this datum was included. This heterogeneity reflects

¹Inanloo et al. (54) presented figures as ng/mL; however, these have been converted to nmol/L for consistency and to facilitate comparison with meta-analysis findings.

the I^2 scores for some analyses, greater than the recommended 25%. However, the P values for those scores are not significant, and we believe that the analysis offers a meaningful contribution to our understanding.

Although the definitions and reporting of vitamin D status permitted direct comparison, it should be noted Christoph et al. (36) used a lower cutoff for sufficiency (>50 nmol/L) (36). As such, women included in our meta-analysis as sufficient in vitamin D were in alternative studies deemed insufficient. However, because this would result in bias toward the null hypothesis, a comparative analysis was included. Given the demonstrated association between vitamin D deficiency and the risk of miscarriage, it is plausible that this may be a dose-dependent relationship whereby women with severe deficiency (<25 nmol/L) are at further increased risk of miscarriage. Only 1 study included degree of deficiency, and therefore, further subgroup analysis was not possible.

There are important factors that influence vitamin D status, including season, ethnicity, and body mass index (3, 57, 58). All observational studies collected data on season of testing, which is not a recognized risk factor for miscarriage. The population levels of vitamin D deficiency vary by latitude—the included observational studies were conducted in Northern Europe, North America, and Australia. The interventional studies were conducted in Iran (2 studies), Egypt, and North America. Ethnicity (independent of the country of birth and latitude) is a strong determinant of vitamin D status. Importantly, ethnicity is also a significant risk factor for vitamin D miscarriage and RM, with Black ethnicities at highest risk (1, 59). This was accounted for in the individual studies by almost all multivariate analyses, with the study by Andersen et al. (40) the only one not to include this.

CONCLUSION

In conclusion, this review adds to current evidence, suggesting women with vitamin D deficiency are at increased risk of miscarriage in addition to other serious reproductive and pregnancy outcomes (6, 7, 60). While our findings strongly endorse future large, well-powered prospective vitamin D supplementation studies, we recommend that these use a pre-defined and consistent set of clinically meaningful definitions and outcomes agreed internationally to specifically target miscarriage prevention (61). We anticipate that whether preconception vitamin D status differentially affects the first and second trimester loss outcomes individually for women with RM and spontaneous loss is likely an important clinical question that remains unanswered.

New evidence-based interventions are required for women at risk of miscarriage (2). Vitamin D deficiency is highly prevalent worldwide with pregnant women at particular risk (62, 63). Although traditionally associated with maternal and newborn bone disease (59, 62, 64), there is now clear recognition of wider detrimental effects, including preterm birth and preeclampsia (6, 7). Given its excellent safety profile and low cost (7), even a small effect of vitamin D would be useful when considering a public health approach. At present, there is a lack of standardized protocols for vitamin D investigation and management for pregnant

women and those preparing to conceive. Compliance with national policy on vitamin D supplementation is also known to be poor; in the United Kingdom, the uptake of antenatal vitamin supplements remains $<20\%$ (59). So, far, vitamin D was only known for its role to prevent late pregnancy complications. This review supports a new perspective on vitamin D in early pregnancy and could help inform women regarding the benefits of early supplementation and treatment compliance. Further well-designed, prospective RCTs addressing preconception and the first trimester vitamin D treatment for women who are vitamin D deficient are recommended.

Preconception vitamin D assessment and treatment of vitamin D deficiency may offer greater benefit than a first trimester approach; however, this systematic review confirms a lack of evidence to support this. Whether early diagnosis and correction of vitamin D deficiency improve pregnancy outcomes for low-risk women or those with RM is unknown. Further high-quality RCTs powered to detect a difference in the risk of miscarriage and RM after preconception vitamin D assessment and treatment are required. Other important questions include whether high-dose vitamin D with rapid correction of vitamin D status confers greater benefit than current nontargeted low-dose vitamin D supplementation strategies. Whether vitamin D status correction improves assisted reproductive technology outcomes and reduces miscarriage risk again remains to be ascertained (13). Moving forward, a clearer, evidence-based strategy for vitamin D supplementation in pregnant women and those planning a pregnancy is required.

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Vitamina D y aborto espontáneo: una revisión sistemática y metaanálisis.

Objetivo: Investigar si existe una asociación significativa entre el nivel de Vitamina D y el riesgo de aborto espontáneo y aborto recurrente (RM).

Diseño: Revisión sistemática y metaanálisis.

Lugar: No aplica.

Pacientes: Mujeres con aborto espontáneo y RM.

Intervenciones: Se realizaron búsquedas en Ovid MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature y el registro central de ensayos controlados Cochrane desde el inicio de la base de datos hasta mayo de 2021. Se incluyeron estudios aleatorizados y observacionales que investigan la asociación entre el nivel de la Vitamina D de la madre y el aborto espontáneo y/o el tratamiento con Vitamina D y el aborto espontáneo.

Medida de resultados principales: El resultado primario fue el aborto espontáneo o RM, utilizando el nivel de Vitamina D como predictor de riesgo. También se evaluó si el tratamiento con Vitamina D reduce el riesgo de aborto espontáneo y RM.

Resultados: De los 902 estudios identificados, se incluyeron 10 ($n = 7.663$ mujeres): 4 ensayos aleatorizados controlados ($n = 666$ mujeres) y 6 estudios observacionales ($n = 6.997$ mujeres). Las mujeres diagnosticadas con deficiencia de Vitamina D (<50 nmol/L) tuvieron un mayor riesgo de aborto espontáneo en comparación con las mujeres con niveles altos de Vitamina D (>75 nmol/L) (odds ratio, 1,94; intervalo de confianza del 95 %, 1,25–3,02; 4 estudios; $n = 3.674$; $I^2 = 18\%$). El análisis combinado, incluyendo a mujeres que tenían insuficiencia (50–75 nmol/L) y deficiencia (<50 nmol/L) de Vitamina D en comparación con mujeres con niveles altos (>75 nmol/L), encontró una asociación con el aborto espontáneo (odds ratio, 1,60; intervalo de confianza del 95%, 1,11–2,30; 6 estudios; $n = 6.338$; $I^2 = 35\%$). Aunque 4 ensayos aleatorizados controlados evaluaron el efecto del tratamiento con Vitamina D sobre el aborto espontáneo, la heterogeneidad del estudio, la calidad de los datos y el sesgo de notificación impidieron la comparación directa y el metaanálisis. La calidad general del estudio fue "baja" o "muy baja" utilizando el enfoque de calificación de recomendaciones, evaluación, desarrollo y evaluaciones.

Conclusiones: Deficiencia o insuficiencia de Vitamina D está asociada con aborto espontáneo. Todavía se desconoce si el tratamiento de Vitamina D previo a la concepción protege contra la pérdida de embarazo en mujeres con riesgo de aborto espontáneo.

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