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

Jennifer A. Tamblyn, M.B.Ch.B., Ph.D.,[a,b,c] Nicole S. P. Pilarski, M.Sc., M.B.B.S.,[c,d] Alexandra D. Markland, B.Med.Sci.,[e] Ella J. Marson, B.Med.Sci.,[e] Adam Devall, Ph.D.,[d,f] Martin Hewison, Ph.D.,[a] Rachel K. Morris, M.B.Ch.B., Ph.D.,[c,d,f] and Arri Coomarasamy, MB.Ch.B., M.D., F.Med.Sci.[a,c]

[a] Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom; [b] CARE Fertility Leeds, Leeds Teaching Hospital Trust, Seacroft Hospital, Leeds, England; [c] Birmingham Women's and Children's Foundation Hospital Trust, Edgbaston, Birmingham, United Kingdom; [d] Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom; [e] College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom; and [f] Birmingham Clinical Trials Unit, University of Birmingham, Birmingham, United Kingdom

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; I^2 = 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; I^2 = 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.
Registration Number: CRD42021259899. (Fertil Steril® 2022;118:111-22. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Vitamin D, miscarriage, recurrent miscarriage

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

Received December 15, 2021; revised and accepted April 8, 2022.
J.A.T. reports grant from Tommy's Charity for the submitted work. M.H. reports speaker fees from DSM/ASN 2021, Danone Mexico 2021, Danone China 2021. R.K.M. reports grant from NIHR PgFAR; payment as a member of the Surepulse clinical advisory board (designs neonatal monitors); RCOG Research, Academic and Scientific Advisory Board, WoW SAC, Tommy's Scientific Advisory Board; and President of the BMFMS outside the submitted work. A.C. reports grant from Tommy's Charity for the submitted work. N.S.P.P.N. has nothing to disclose. A.d.M. has nothing to disclose. E.J.M. has nothing to disclose. A.D. has nothing to disclose.
Reprint requests: Jennifer A. Tamblyn, M.B.Ch.B., Ph.D., Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, B15 2TT (E-mail: j.tamblyn@bham.ac.uk).

Fertility and Sterility® Vol. 118, No. 1, July 2022 0015-0282

https://doi.org/10.1016/j.fertnstert.2022.04.017

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

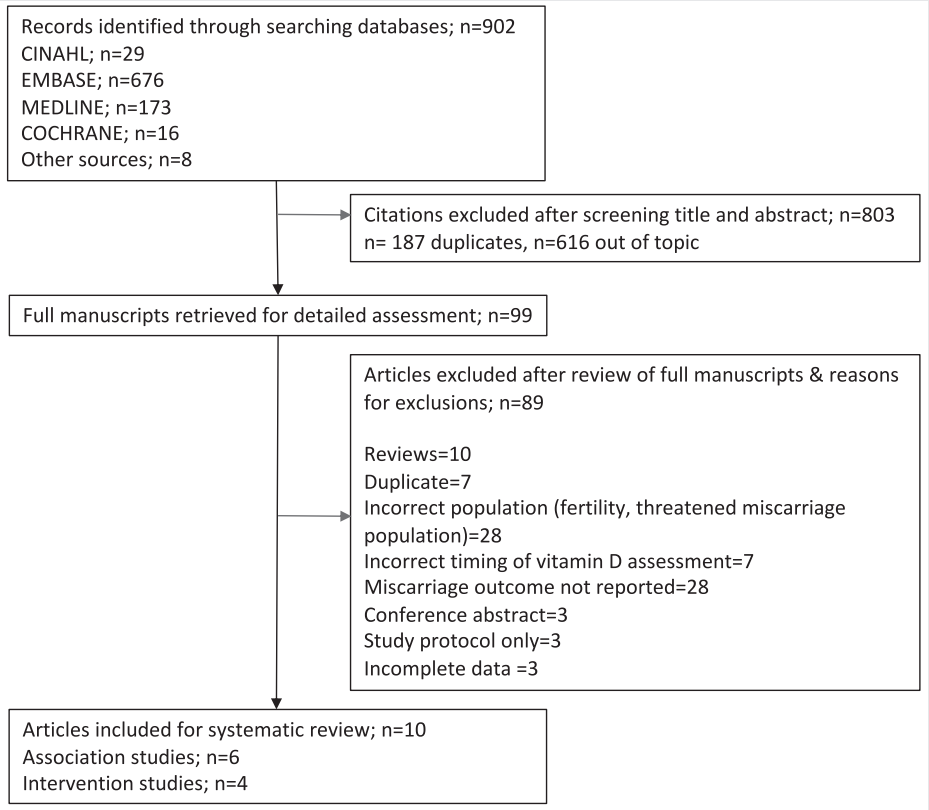
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the review process is illustrated in Figure 1. The search yielded 894 citations and a further 8 identified from other sources. Of these, 803 were excluded (n = 187 duplicates, n = 616 out of topic) because it was clear 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



Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study selection. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of literature search results and included and excluded studies.

Tamblyn. Vitamin D and miscarriage. Fertil Steril 2022.

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 ± 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 (n = 58); median 25(OH)D nmol/L, 55.6 (IQR, 43.60–69.92)	Missed, complete or incomplete miscarriage, or blighted ovum at <22 wk of GA	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%)	Pregnancy 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%	Spontaneous 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 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

Tamblyn. Vitamin D and miscarriage. Fertil Steril 2022.

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)	Deficient, <20.9 ng/mL (52.3 nmol/L); 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%)	Spontaneous abortion at <20 wk of GA	Electronic health care 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.

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?

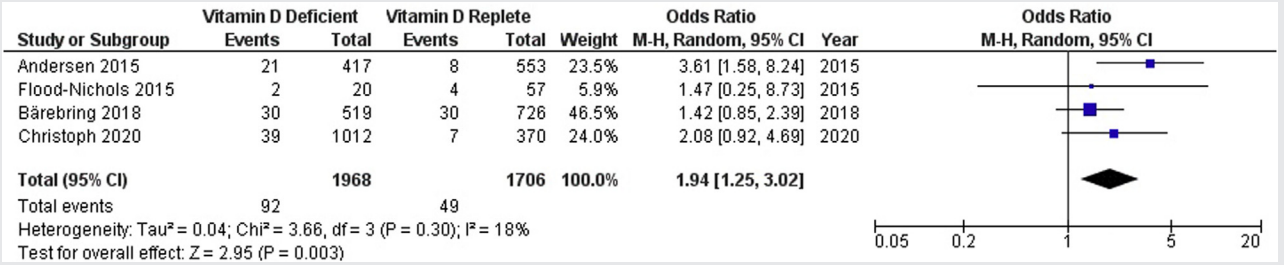
Study overview. Overall, 4 RCT studies met the initial inclusion criteria (46–49), with a systematic assessment detailed for reference (Supplemental Table 1). Overall, the sample sizes were small (n = <100), except that in the study by Hollis et al. (46) (n = 502). In 3 RCTs, the population of interest 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 (1α-hydroxyvitamin D3 prodrug, 0.25 μg 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 $1\alpha,25(OH)_2D_2$, is ordinarily reserved for patients with renal insufficiency and/or renal 1α-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.

Tamblyn. 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).

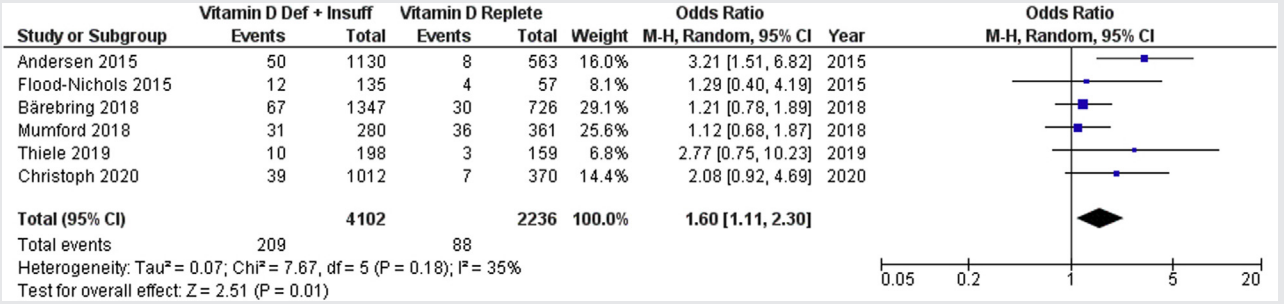
DISCUSSION

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.

Tamblyn. Vitamin D and miscarriage. Fertil Steril 2022.

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 placentae (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/L[1]) (20/23, 87.0%) and lower mean 25(OH)D3 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).

[1] Inanloo 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.

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

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 predefined 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.

Acknowledgments: The authors thank Derek Yates, who assisted with the literature search, and Mona Soleymani and Olga Usacheva, who assisted with full-text translation of non-English manuscripts screened as potentially eligible for inclusion (54).

DIALOG: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/34425

REFERENCES

1. Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet 2021;397:1658–67.
2. Coomarasamy A, Dhillon-Smith RK, Papadopoulou A, Al-Memar M, Brewin J, Abrahams VM, et al. Recurrent miscarriage: evidence to accelerate action. Lancet 2021;397:1675–82.
3. Kramer CK, Ye C, Swaminathan B, Hanley AJ, Connelly PW, Sermer M, et al. The persistence of maternal vitamin D deficiency and insufficiency during pregnancy and lactation irrespective of season and supplementation. Clin Endocrinol (Oxf) 2016;84:680–6.
4. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911–30.
5. van Schoor NM, Lips P. Worldwide vitamin D status. Best Pract Res Clin Endocrinol Metab 2011;25:671–80.
6. Chu J, Gallos I, Tobias A, Tan B, Eapen A, Coomarasamy A. Vitamin D and assisted reproductive treatment outcome: a systematic review and meta-analysis. Hum Reprod 2018;33:65–80.

7. De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev 2016:CD008873.
8. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol 2014;144 Pt A:138–45.
9. Zhou SS, Tao YH, Huang K, Zhu BB, Tao FB. Vitamin D and risk of preterm birth: up-to-date meta-analysis of randomized controlled trials and observational studies. J Obstet Gynaecol Res 2017;43:247–56.
10. Pacis MM, Fortin CN, Zarek SM, Mumford SL, Segars JH. Vitamin D and assisted reproduction: should vitamin D be routinely screened and repleted prior to ART? A systematic review. J Assist Reprod Genet 2015; 32:323–35.
11. Zhao J, Huang X, Xu B, Yan Y, Zhang Q, Li Y. Whether vitamin D was associated with clinical outcome after IVF/ICSI: a systematic review and meta-analysis. Reprod Biol Endocrinol 2018;16:13.
12. Cozzolino M, Busnelli A, Pellegrini L, Riviello E, Vitagliano A. How vitamin D level influences in vitro fertilization outcomes: results of a systematic review and meta-analysis. Fertil Steril 2020;114:1014–25.
13. Paffoni A, Somigliana E, Sarais V, Ferrari S, Reschini M, Makieva S, et al. Effect of vitamin D supplementation on assisted reproduction technology (ART) outcomes and underlying biological mechanisms: protocol of a randomized clinical controlled trial. The "supplementation of vitamin D and reproductive outcome" (SUNDRO) study. BMC Pregnancy Childbirth 2019;19:395.
14. Zehnder D, Evans KN, Kilby MD, Bulmer JN, Innes BA, Stewart PM, et al. The ontogeny of 25-hydroxyvitamin D(3) 1alpha-hydroxylase expression in human placenta and decidua. Am J Pathol 2002;161:105–14.
15. Tamblyn JA, Susarla R, Jenkinson C, Jeffery LE, Ohizua O, Chun RF, et al. Dysregulation of maternal and placental vitamin D metabolism in preeclampsia. Placenta 2017;50:70–7.
16. Chan SY, Susarla R, Canovas D, Vasilopoulou E, Ohizua O, McCabe CJ, et al. Vitamin D promotes human extravillous trophoblast invasion in vitro. Placenta 2015;36:403–9.
17. Ganguly A, Tamblyn JA, Finn-Sell S, Chan SY, Westwood M, Gupta J, et al. Vitamin D, the placenta and early pregnancy: effects on trophoblast function. J Endocrinol 2018;236:R93–103.
18. Zhang JY, Wu P, Chen D, Ning F, Lu Q, Qiu X, et al. Vitamin D promotes trophoblast cell induced separation of vascular smooth muscle cells in vascular remodeling via induction of G-CSF. Front Cell Dev Biol 2020;8:601043.
19. Teklenburg G, Salker M, Heijnen C, Macklon NS, Brosens JJ. The molecular basis of recurrent pregnancy loss: impaired natural embryo selection. Mol Hum Reprod 2010;16:886–95.
20. Woods L, Perez-Garcia V, Hemberger M. Regulation of placental development and its impact on fetal growth-new insights from mouse models. Front Endocrinol (Lausanne) 2018;9:570.
21. Ball E, Bulmer JN, Ayis S, Lyall F, Robson SC. Late sporadic miscarriage is associated with abnormalities in spiral artery transformation and trophoblast invasion. J Pathol 2006;208:535–42.
22. Dimitriadis E, Menkhorst E, Saito S, Kutteh WH, Brosens JJ. Recurrent pregnancy loss. Nat Rev Dis Primers 2020;6:98.
23. Lucas ES, Vrljicak P, Muter J, Diniz-da-Costa MM, Brighton PJ, Kong CS, et al. Recurrent pregnancy loss is associated with a pro-senescent decidual response during the peri-implantation window. Commun Biol 2020;3: 37.
24. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
25. Hipp H, Crawford S, Kawwass JF, Chang J, Kissin DM, Jamieson DJ. First trimester pregnancy loss after fresh and frozen in vitro fertilization cycles. Fertil Steril 2016;105:722–8.
26. Wang JX, Davies MJ, Norman RJ. Polycystic ovarian syndrome and the risk of spontaneous abortion following assisted reproductive technology treatment. Hum Reprod 2001;16:2606–9.
27. Hu L, Du J, Lv H, Zhao J, Chen M, Wang Y, et al. Influencing factors of pregnancy loss and survival probability of clinical pregnancies conceived through assisted reproductive technology. Reprod Biol Endocrinol 2018;16:74.
28. Winter E, Wang J, Davies MJ, Norman R. Early pregnancy loss following assisted reproductive technology treatment. Hum Reprod 2002;17:3220–3.
29. Farr SL, Schieve LA, Jamieson DJ. Pregnancy loss among pregnancies conceived through assisted reproductive technology, United States, 1999-2002. Am J Epidemiol 2007;165:1380–8.
30. Mumford SL, Garbose RA, Kim K, Kissell K, Kuhr DL, Omosigho UR, et al. Association of preconception serum 25-hydroxyvitamin D concentrations with livebirth and pregnancy loss: a prospective cohort study. Lancet Diabetes Endocrinol 2018;6:725–32.
31. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366: l4898.
32. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed May 9, 2022.
33. Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S, et al. Panethnic differences in blood pressure in Europe: a systematic review and meta-analysis. PLoS One 2016;11:e0147601.
34. Alshabanat A, Zafari Z, Albanyan O, Dairi M, FitzGerald JM. Asthma and COPD overlap syndrome (ACOS): a systematic review and meta analysis. PLoS One 2015;10:e0136065.
35. Herzog R, Álvarez-Pasquin MJ, Díaz C, Del Barrio JL, Estrada JM, Gil Á. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Public Health 2013;13:154.
36. Christoph P, Challande P, Raio L, Surbek D. High prevalence of severe vitamin D deficiency during the first trimester in pregnant women in Switzerland and its potential contributions to adverse outcomes in the pregnancy. Swiss Med Wkly 2020;150:w20238.
37. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook: introduction to GRADE handbook. Available at: http://guidelinedevelopment.org/handbook. Accessed May 9, 2022.
38. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
39. The Cochrane Collaboration Review Manager (RevMan) [Computer program], Version 5.4. Available at: https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-non-cochrane-reviews. Accessed May 9, 2022.
40. Andersen LB, Jørgensen JS, Jensen TK, Dalgård C, Barington T, Nielsen J, et al. Vitamin D insufficiency is associated with increased risk of first-trimester miscarriage in the Odense Child Cohort. Am J Clin Nutr 2015;102: 633–8.
41. Møller UK, Streym S, Heickendorff L, Mosekilde L, Rejnmark L. Effects of 25OHD concentrations on chances of pregnancy and pregnancy outcomes: a cohort study in healthy Danish women. Eur J Clin Nutr 2012;66:826–8.
42. Jabber YM, Hassan AJ, Abdullah HN. Assessment of some biomarkers related with recurrent miscarriages in Iraq. Sys Rev Pharm 2020;11:156–62.
43. Bärebring L, Bullarbo M, Glantz A, Hulthen L, Ellis J, Jagner A, et al. Trajectory of vitamin D status during pregnancy in relation to neonatal birth size and fetal survival: a prospective cohort study. BMC Pregnancy Childbirth 2018;18:51.
44. Flood-Nichols SK, Tinnemore D, Huang RR, Napolitano PG, Ippolito DL. Vitamin D deficiency in early pregnancy. PLoS One 2015;10:e0123763.
45. Thiele DK, Erickson EN, Snowden JM. High prevalence of maternal serum 25-hydroxyvitamin D deficiency is not associated with poor birth outcomes among healthy white women in the Pacific Northwest. J Obstet Gynecol Neonatal Nurs 2019;48:163–75.
46. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. J Bone Miner Res 2011;26:2341–57.
47. Rafiee M, Gharagozloo M, Ghahiri A, Mehrabian F, Maracy MR, Kouhpayeh S, et al. Altered Th17/Treg ratio in recurrent miscarriage after treatment with paternal lymphocytes and vitamin D3: a double-blind placebo-controlled study. Iran J Immunol 2015;12:252–62.
48. Samimi M, Foroozanfard F, Amini F, Sehat M. Effect of vitamin D supplementation on unexplained recurrent spontaneous abortion: a double-blind randomized controlled trial. Glob J Health Sci 2016;9:95.

49. Ibrahim ZM, Madany EH, Abdel Aal RM, El Biely MM. Role of 1,25-dihydroxyvitamin D (vitamin D3) as immunomodulator in recurrent missed miscarriage. Middle East Fertil Soc J 2013;18:171–6.
50. Jean G, Souberbielle JC, Chazot C. Vitamin D in chronic kidney disease and dialysis patients. Nutrients 2017;9:328.
51. Guo J, Liu S, Wang P, Ren H, Li Y. Characterization of VDR and CYP27B1 expression in the endometrium during the menstrual cycle before embryo transfer: implications for endometrial receptivity. Reprod Biol Endocrinol 2020;18:24.
52. Adams JS, Hewison M. Extrarenal expression of the 25-hydroxyvitamin D-1-hydroxylase. Arch Biochem Biophys 2012;523:95–102.
53. Hou W, Yan XT, Bai CM, Zhang XW, Hui LY, Yu XW. Decreased serum vitamin D levels in early spontaneous pregnancy loss. Eur J Clin Nutr 2016;70:1004–8.
54. Inanloo M, Keshavarz EZ, Naeiji Z, Asgari M. Comparison of serum vitamin D levels in threatened abortion patients and women with normal pregnancy. Iran J Obstet Gynecol Infertil 2019;22:49–57.
55. Amegah AK, Klevor MK, Wagner CL. Maternal vitamin D insufficiency and risk of adverse pregnancy and birth outcomes: a systematic review and meta-analysis of longitudinal studies. PLoS One 2017;12:e0173605.
56. Stokes CS, Lammert F, Volmer DA. Analytical methods for quantification of vitamin D and implications for research and clinical practice. Anticancer Res 2018;38:1137–44.
57. Darling AL, Hart KH, Macdonald HM, Horton K, Kang'ombe AR, Berry JL, et al. Vitamin D deficiency in UK South Asian women of childbearing age: a comparative longitudinal investigation with UK Caucasian women. Osteoporos Int 2013;24:477–88.
58. Hauta-Alus HH, Holmlund-Suila EM, Rita HJ, Enlund-Cerullo M, Rosendahl J, Valkama SM, et al. Season, dietary factors, and physical activity modify 25-hydroxyvitamin D concentration during pregnancy. Eur J Nutr 2018;57:1369–79.
59. Uday S, Naseem S, Large J, Denmeade R, Goddard P, Preece MA, et al. Failure of national antenatal vitamin D supplementation programme puts dark skinned infants at highest risk: a newborn bloodspot screening study. Clin Nutr 2021;40:3542–51.
60. Chu J, Gallos I, Tobias A, Robinson L, Kirkman-Brown J, Dhillon-Smith R, et al. Vitamin D and assisted reproductive treatment outcome: a prospective cohort study. Reprod Health 2019;16:106.
61. Smith P, Cooper N, Dhillon-Smith R, O'Toole E, Clark TJ, Coomarasamy A. Core Outcome Sets in Miscarriage Trials (COSMisT) study: a study protocol. BMJ Open 2017;7:e018535.
62. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab 2016;101:394–415.
63. Płudowski P, Karczmarewicz E, Bayer M, Carter G, Chlebna-Sokół D, Czech-Kowalska J, et al. Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe - recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol Pol 2013;64:319–27.
64. Uday S, Fratzl-Zelman N, Roschger P, Klaushofer K, Chikermane A, Saraff V, et al. Cardiac, bone and growth plate manifestations in hypocalcemic infants: revealing the hidden body of the vitamin D deficiency iceberg. BMC Pediatr 2018;18:183.

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 espontaneo 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.

Número de Registro del Ensayo Clínico: CRD42021259899.