How vitamin D level influences in vitro fertilization outcomes: results of a systematic review and meta-analysis

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Objective: To investigate the impact of serum vitamin D level on in vitro fertilization (IVF) outcomes.
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patients: Infertile women undergoing conventional IVF or intracytoplasmic sperm injection (ICSI).
Interventions: Systematic search of PubMed, MEDLINE, EMBASE, Global Health, The Cochrane Library, Health Technology Assessment Database, and Web of Science from inception until July 2019 with cross-checking of references from relevant articles in English. Vitamin D levels were categorized into three groups: deficient (<20 ng/mL), insufficient (20–30 ng/mL), and replete (>30 ng/mL). Before starting the data extraction, we registered the review protocol in PROSPERO (CRD42019134258).
Main Outcome Measures: We consider clinical pregnancy rate (CPR), live birth rate (LBR), and/or ongoing pregnancy rate (OPR) as primary outcomes. Likewise, the miscarriage rate was considered as a secondary outcome.
Results: Primary analysis showed that women with a replete level of vitamin D had higher CPR and LBR/OPR compared to those with a deficient of insufficient level of vitamin D. However, sensitivity analysis led to non-significant differences between the comparators for CPR (odds ratio 0.71, 95% confidence interval 0.47–1.08, I2 = 61%) and OPR/LBR (odds ratio 0.78, 95% confidence interval 0.56–1.08], I2 = 61%). Also, for miscarriage a statistically different rate was not reached.
Conclusion: Serum vitamin D levels do not influence IVF outcomes in terms of CPR, LBR/OPR, and miscarriage rate. Future large cohort studies are warranted to determine whether the threshold of vitamin D affects reproductive outcomes. Currently, there is a lack of consensus between the appropriate vitamin D threshold to predict reproductive outcomes compared to the one established for bone health.
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El resumen está disponible en Español al final del artículo.

Key Words: Vitamin D, live birth, in vitro fertilization, endometrial receptivity, assisted reproductive treatments

Vitamin D is a fat-soluble steroid hormone. It is produced endogenously by the skin in response to ultraviolet B rays, resulting from the conversion of 7-dehydrocholesterol. Approximately 80% of the vitamin D ratio is derived from skin production, whereas only 20% is obtained through diet (1). Physiologically, vitamin D is involved primarily in the regulation of calcium–phosphorus homeostasis and the promotion of bone mineralization (2). In the female reproductive system, vitamin D seems to have several autocrine, paracrine, and endocrine functions. These include regulation of ovarian and endometrial cell proliferation and the expression of genes involved in endometrial receptivity (3, 4). Interestingly, knock-out mice with blocked vitamin D receptor genes developed defective folliculogenesis and morphological alterations of

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the uterus. This suggests that vitamin D might affect embryogenesis and follicle development (5). Furthermore, vitamin D seems to modulate primary follicle recruitment through regulation of antimüllerian hormone production (6, 7). Vitamin D deficiency is common among infertile couples. In fact, it has been estimated that approximately 15% of the infertile population has low vitamin D levels, with a higher prevalence among female partners (8, 9). Recent insights about a potential association between specific infertility-related disorders in women, such as endometriosis and polycystic ovary syndrome and vitamin D insufficiency (10, 11), support a possible link with infertility.

Vitamin D appears to play a role in the physiology of the female reproductive system. Nevertheless, the way in which vitamin D may affect the results of assisted reproductive technology is still uncertain. On one hand, some studies showed no association between vitamin D levels and in vitro fertilization (IVF) success (12–17). On the other hand, other studies found a negative association between vitamin D insufficiency or deficiency and embryo quality, clinical pregnancy rate, and ongoing pregnancy rate after IVF (8, 9, 18, 19). Thus, the purpose of this systematic review and meta-analysis was to investigate the possible association between vitamin D serum levels and IVF outcomes.

MATERIALS AND METHODS

Study Design

This study refers to a systematic review and meta-analysis of all studies investigating the impact of serum vitamin D on IVF outcomes (i.e., live birth rate [LBR]/ ongoing pregnancy rate [OPR], clinical pregnancy rate [CPR], and miscarriage rate [MR]). All of the designs, interpretations of data, drafting, and revisions were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (20, 21), available through the Enhancing the Quality and Transparency of Health Research network. Before starting the data extraction, we registered the review protocol in PROSPERO (CRD42019134258).

Search Strategy

From the study's inception until July 2019, we performed a literature search in PubMed, MEDLINE, EMBASE, Global Health, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register), Health Technology Assessment Database and Web of Science. The search strategy included a combination of the Medical Subject Headings: one including terms for vitamin D (vitamin D, 25-hydroxy vitamin D, 25(OH)D OR 1,25-(OH)2D), and the second including terms for reproductive techniques (IVF OR ICSI OR ARTs).

Inclusion Criteria

We included published observational studies (i.e., retrospective or prospective cohort studies, case-control studies, cross-sectional studies, and case series). Likewise, we categorized vitamin D levels into three groups: deficient (<20 ng/mL), insufficient (20−30 ng/mL), and replete (>30 ng/mL).

Study Outcomes and Outcomes Measures

The outcomes considered in the meta-analysis were as follows: CPR per woman, defined as pregnancy diagnosed by ultrasonographic intrauterine visualization of one or more gestational sacs; OPR per woman, defined as pregnancy beyond 24 weeks' gestation; or LBR per woman, defined as the number of deliveries that resulted in at least one live-born infant; and MR per clinical pregnancy, defined as a fetal loss before the 20 weeks' gestation.

Study Selection and Data Extraction

We retrieved and systematically reviewed all pertinent articles and their respective reference lists to identify further reports that could be included in the meta-analysis. Moreover, we consulted both review articles and meta-analyses published on the impact of serum vitamin D concentration on IVF outcomes in the same period. In the same way, we searched their reference lists for potential additional studies. No attempt was carried out to identify unpublished studies. To exclude what are considered irrelevant citations, two authors (M.C., A.V.) independently performed an initial screening of title and abstract of all. In case of doubt, studies were discussed in consensus meetings with two other authors (L.P., A.B.). When available, information on adjusted confounders and adjusted risk estimates was collected. When possible, all authors were contacted for missing data.

Assessing Risk of Bias

Two reviewers (M.C., A.V.) independently judged the methodological quality of studies included in the meta-analysis. We used a modified version of the Newcastle−Ottawa Scale. Thus, we evaluated the quality of studies through five different domains: "sample representativeness," "sampling technique," "assessment of vitamin D status," "quality of the population's description," and "incomplete outcome data" (Supplemental Table 1). According to the total number of points assigned, each study was categorized to be either at a low (three or fewer points) or at a high risk of bias (more than three points). Any discrepancies concerning the authors' judgments were referred to a third reviewer (L.P.) and resolved by consensus.

Data Analysis

Two authors (M.C., A.V.) completed the meta-analysis using Review Manager (RevMan), Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Correspondingly, they conducted a statistical analysis using the generic inverse variance method. There, they determined a pooled odds ratio (OR) from the natural logarithm (LN) of the studies' individual OR [LN (OR)] and the 95% confidence interval (CI). The standard error of the mean for the LN (OR) was calculated from the 95% CI using the following formula: standard error of the mean = [LN (upper CI limit) LN (lower CI limit)]/3.92, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (21). Statistical heterogeneity was assessed by I2 statistics. Furthermore, they reported graphically the

pooled estimates with forest plots. For each study outcome, the meta-analysis included the following comparisons: serum replete level of vitamin D (≥ 30 ng/mL) versus insufficient or deficient level of Vitamin D (<30 ng/mL); serum replete or insufficient level of vitamin D (≥20 ng/mL) versus deficient level of vitamin D (<20 ng/mL); serum replete level of vitamin D (≥ 30 ng/mL) versus insufficient level of vitamin D (<30 ng/mL and ≥ 20 ng/mL); serum replete level of vitamin D (≥ 30 ng/mL) versus deficient level of vitamin D (<20 ng/mL); and serum insufficient level of vitamin D (<30 ng/mL and ≥ 20 ng/mL) versus deficient level of vitamin D (<20 ng/mL).

With regard to sensitivity, they explored both sources of heterogeneity (i.e., by serially excluding each study and different study subgroups according to their methodological quality scores, and adjusting results for statistically proven confounders), as well as subgroup analyses (i.e., splitting studies according to the type of IVF cycle [homologous IVF cycles, egg donation IVF cycles]). They measured the inconsistency of studies' results using the Cochrane Q and the *I2* statistics (22). Negative values of *I2* are set equal to 0 so that *I2* lies between 0% and 100%. According to the *Cochrane Handbook for Systematic Reviews of Interventions*, the level of heterogeneity may change depending on the I2 level. An I2 value of 0% indicates no observed heterogeneity, I2 values from 30% to 60% may represent moderate heterogeneity, I2 values from 50% to 90% may indicate substantial heterogeneity, and I2 values from 75% to 100% express considerable heterogeneity (22,23).

RESULTS

Results of Search and Description of Studies

The literature search yielded 4200 records, and 1160 of those were removed due to duplications. Later, we reviewed the titles and abstracts and we identified 59 studies as potentially eligible for inclusion. Consequently, we excluded 10 systematic and narrative reviews, as well as 24 publications because they were not in line with the review, and five original studies because their principal outcomes were on male infertility. Moreover, three were excluded because they evaluated the association between deficient vitamin D in follicular fluid and IVF outcomes: one did not produce results of enough quality to be included in the meta-analysis, and the outcomes of the other studies did not apply to the scope of our meta-analysis. After the evaluation of the full text, we excluded 45 studies. Finally, a total number of 14 studies (9,11-14,17-19,24-29) were included in the present meta-analysis (Supplemental Fig. 1).

The 14 studies included a total number of 4,382 participants. Table 1 includes a summary of the main characteristics of these studies. Nevertheless, seven of them were retrospective studies and seven were prospective studies. Likewise, three studies included women who were donor egg recipients.

Assessment of vitamin D serum levels. Vitamin D status was determined by measuring the serum levels of 25-hydroxy vitamin D. Three of the included studies (9,19,25) assessed vitamin D before starting the treatment cycle, whereas two other studies assessed vitamin D before oocyte retrieval (17,18). Two more study assessed vitamin D at the time of oocyte retrieval (11,24), one study the day of trigger ovulation (13) whereas another study assessed vitamin D before embryo transfer (14). Finally, a further five studies (12,26-29) measured vitamin D during the precycle, but it was not clearly defined.

Risk of Bias Assessment

Supplemental Table 1 summarizes the risk of bias assessment. Studies were at a low risk for bias for sample representativeness when they reached a sample size of at least 250 patients. Studies with an adequate sampling strategy (random or consecutive) were at a low risk for bias. Studies in which vitamin D was assessed before the start of ovarian stimulation were at a low risk for bias.

Studies that assessed vitamin D during ovarian stimulation, triggering, oocyte retrieval, or embryo transfer were at a high risk for bias. Moreover, studies were also categorized as having a high risk of bias when there was a lack of information on IVF-ET protocols, in terms of quality of the population's description. Likewise, studies with incomplete data outcomes were also categorized as high risk.

Primary Analysis

Clinical Pregnancy Rate

Replete level of vitamin D (≥ 30 ng/mL) versus insufficient or deficient level of vitamin D (<30 ng/mL). We meta-analyzed a total of 2,053 participants (n = 479 with a replete level of vitamin D and n = 1,574 with an insufficient or deficient level of vitamin D) from 8 studies (9,11-13,17,25,27,28). Women with vitamin D ≥30 ng/mL had higher CPR compared to patients with vitamin D <30 ng/mL (OR 0.68, 95% CI 0.48−0.98, I2 = 57%, *P*=.04) (Fig. 1A).

Replete or insufficient level of vitamin D (≥ 20 ng/mL) versus deficient level of vitamin D (<20 ng/mL). We included a total number of 2284 participants (n = 1,271 with a replete or insufficient level of vitamin D and n = 1,013 with a deficient level of vitamin D) from nine studies (9,12,13,18,19,24-26,28). No difference between comparators was found (OR 0.80, 95% CI 0.56−1.15, I2 = 70%, *P*=.23) (Fig. 1B).

Replete level of vitamin D (≥ 30 ng/mL) versus insufficient level of vitamin D (<30 ng/mL and ≥ 20 ng/mL). We analyzed a total of 812 participants (n = 308 with an adequate level of vitamin D and n = 504 with an insufficient level of vitamin D) from five studies (9,12,13,25,28). No difference between comparators was found (OR 0.77, 95% CI 0.48−1.21, I2 = 51%, *P*=.25).

Replete level of vitamin D (≥ 30 ng/mL) versus deficient level of vitamin D (<20 ng/mL). We meta-analyzed 615 participants (n = 250 with a replete level of vitamin D and n = 365 with a deficient level of vitamin D) from four studies (9,12,13,28). No statistical difference was found between groups (OR 0.72, 95% CI 0.37−1.41, I2 = 66%, *P*=.34).

TABLE 1

General characteristic of the studies included in the meta-analysis.

Author(s), year	Study design, country, and time of realization	Participants (n) and main inclusion criteria	Exclusion criteria	Ovarian stimulation (drugs)	Intervention and timing	Vitamin D categorization
Garbedian et al., 2013	Retrospective cohort study	173 Patients undergoing IVF cycles; age 18–41 y, FSH ≤12 IU/L	Donor oocytes, congenital/acquired uterine anomalies	Long luteal agonist protocol; microdose flare protocol; antagonist protocol started as per flexible start protocol; rFSH ± LH or hMG;trigger with 10,000 IU of hCG when three or more follicles >17 mm were achieved	162 ETs; embryo transfer day 3 or 5; vaginal micronized progesterone for luteal phase support	Sufficient vitamin D ≥75 nmol/L ; insufficient vitamin D <75 nmol/L
Franasiak et al., 2015	Retrospective cohort study	529 Patients; comprehensive chromosome screening		Urinary FSH or recombinant FSH and rLH or hMG along with GnRH agonist (long down-regulation or microdose flare) or GnRH antagonist; trigger with: recombinant hCG 500 μg; or purified urinary hCG 10,000 IU or GnRH agonist (leuprolide acetate 2 mg) ± 1,500 IU of hCG when two or three follicles reached 17–18 mm	517 Euploid fresh or cryopreserved embryo transfers; fresh ET on day 6; luteal support with vaginal progesterone	Replete vitamin D ≥30 ng/mL; insufficient vitamin D20–29.9 ng/mL; deficient vitamin D<20 ng/mL
Firouzabadi et al., 2013	Prospective observational study	180 Patients; FSH baseline <10 IU/L; age 20–39 y	Liver, kidney, heart disease; severe male factor; endometriosis; Cushing syndrome; Hyper- or hypothyroidism; hyperprolactinemia; BMI >29 or <18	Long protocol; rFSH according to patient's age and follicular count; trigger with hCG 10,000 IU	495 ETs	Sufficient vitamin D 30–100 ng/mL; insufficient vitamin D 10–29 ng/mL; deficient vitamin D <10 ng/mL
Ciepiela et al., 2018	Prospective cohort study	198 Patients; age 18–38 y	Hydrosalpinx; moderate (5–10 mln sperms/mL) and severe (<5 mln sperm/mL) male infertility; poor ovarian response	Antagonist protocol; agonist protocol; ICSI	88 Single fresh ETs on day 3 and 18 ETs on day 5	Deficient vitamin D <20 ng/mL; sufficient vitamin D ≤20 ng/mL

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TABLE 1

Continued.

Author(s), year	Study design, country, and time of realization	Participants (n) and main inclusion criteria	Exclusion criteria	Ovarian stimulation (drugs)	Intervention and timing	Vitamin D categorization
Rudick et al., 2014	Retrospective cohort study	99 Recipients of egg donation		Agonist protocol; antagonist protocols with flexible start; rFSH alone or in combination with hMG; trigger with hCG 10,000 IU; IVF and/or ICSI; recipient down-regulation with GnRH agonist; endometrial preparation with E2 either orally or via patches starting 4 days before donor's ovarian stimulation	Endometrial thickness of 7 mm fresh ET on days 3 or 5; luteal phase supplementation with vaginal micronized progesterone	Replete vitamin D >30 ng/mL; insufficient vitamin D 20–30 ng/mL; deficient vitamin D <20 ng/mL
Fabris et al., 2014	Retrospective study	267 Patients; age 29–49 y; BMI 15–38 kg/m^2; normal karyotype	Family history/hereditary chromosomal diseases; Endometriosis III–IV; PCOS; hydrosalpinx; uterine abnormalities; partner's azoospermia		ET on day 3; previous down-regulation with single-dose GnRH agonist depot; after menses E2 valerate 2–6 mg daily; micronized progesterone 800 mg/d vaginally from day of oocyte donation	Replete vitamin D >30 ng/mL; deficient vitamin D 20–30 ng/mL; insufficient vitamin D <20 ng/mL
Fru et al., 2014	Retrospective study	102 Women undergoing IVF				Deficient <50 nmol/L; insufficient 50–75 nmol/L; replete >75 nmol/L
Chu et al., 2019	Prospective cohort observational	464 Women undergoingIVF		GnRH antagonist; GnRH agonist; stimulation: rFSH/hp-hMG; trigger with hCG (6.500)	Single ET day 5	Deficient <50 nmol/L; insufficient 50–75 nmol/L; replete >75 nmol/L
Polyzos et al., 2014	Retrospective cohort study	368 Women; age 18–36 y	Previous cycle canceled; preimplantation genetic testing	GnRH antagonist; GnRH agonist; stimulation: rFSH/hp-hMG, corifollitropin alfa; trigger with hCG (5,000–10,000)	Single ET day 5	Deficient vitamin D <20 ng/mL; insufficient vitamin D 20–30 ng/mL; replete vitamin D >30 ng/mL

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TABLE 1

Continued.

Author(s), year	Study design, country, and time of realization	Participants (n) and main inclusion criteria	Exclusion criteria	Ovarian stimulation (drugs)	Intervention and timing	Vitamin D categorization
Rudick et al., 2012	Retrospective cohort study	188 Infertile women undergoing their first IVF treatment	Previous IVF cycles; zygote intrafallopian tube transfer	GnRH agonist; antagonist flexible protocol; rFSH alone or in association with hMG; trigger with 10,000 hCG; IVF and/or ICSI	Fresh ET on days 3–5;luteal phase supplementation with vaginal micronized progesterone	Deficient vitamin D <20 ng/mL; insufficient vitamin D 20–30 ng/mL; replete vitamin D >30 ng/mL
Paffoni et al., 2014	Prospective cross-sectional study	480 Women; 145 patients did not undergo fresh ET; age 18–42 y; BMI 18–25 kg/m^2; fresh ET	History of malignancy; hypertension; diabetes; multiple sclerosis; autoimmune disorders	Long protocol; GnRH antagonist protocol; flare-up protocol	335 fresh ETs	Vitamin D <20 ng/mL; vitamin D ≥20 ng/mL
Banker et al., 2017	Prospective cohort observational	291Women; Group A recipients (n = 192); Group B donors (n = 99)	Celiac disease; Crohn's disease; hyperparathyroidism; active malignancy; previous RT or CT	Group A endometrial preparation with E2 valerate tablets 4–8 mg/d; endometrial thickness of 7 mm	Vaginal micronized progesterone 400 mg twice per d; ET on day 3 or 5	Deficient vitamin D: <20 ng/mL; replete–insufficient vitamin D 20 to ≥30 ng/mL
van de Vijver et al., 2016	Prospective observational cohort	280 Patients; age 18–39 y	Embryo transfer on day 3; women with uterine abnormalities, endocrine disorders, severe endometriosis; repeated implantation failure	Endometrial preparation with using E2 valerate at 2 mg twice per day for 7 days, followed by 6 days of E2 valerate at a dose of 2 mg threetimes per day	Endometrial thickness ≥7 mm; ET on day 5; vaginal micronized progesterone 400 mg twice per day	Vitamin D <20 ng/mL; vitamin D ≥20 ng/mL
Chatzicharalampous et al., 2017	Retrospective cohort study	763 Patients; age <40 y	Embryo transfer on day 3		Single ET day 5	Replete vitamin D: ≥30 ng/mL; insufficient vitamin D 20–29.9 ng/mL; deficient vitamin D <20 ng/mL

Note: BMI = body mass index; CT = chemotherapy; ET = embryo transfer; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; hMG = human menopausal gonadotropin; hp = highly-purified; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; LH = luteinizing hormone; mln = million; PCOS = polycystic ovary syndrome; rFSH = recombinant follicle-stimulating hormone; rLH = recombinant luteinizing hormone; RT = radiotherapy.

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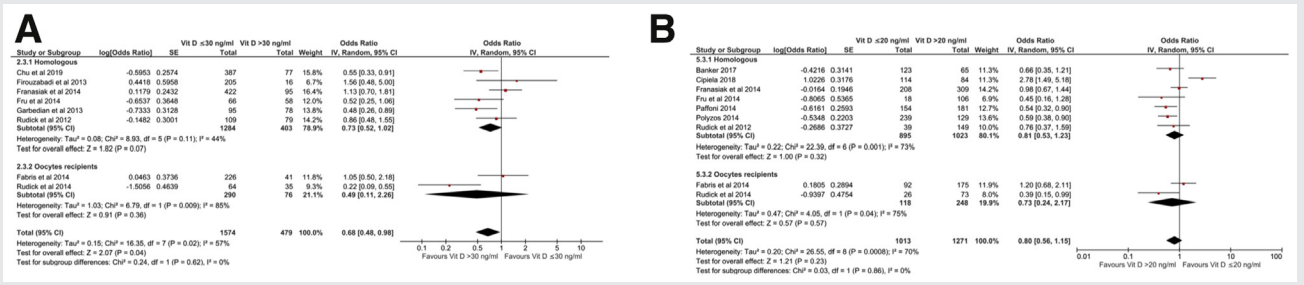
FIGURE 1



Clinical pregnancy rate. (**A**) Replete levels of vitamin D (≥30 ng/mL) versus insufficient or deficient levels of vitamin D (<30 ng/mL). (**B**) Replete or insufficient levels of vitamin D (≥20 ng/mL) versus deficient levels of vitamin D (<20 ng/mL).

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Insufficient level of vitamin D (<30 ng/mL and ≥20 ng/mL) versus deficient level of vitamin D (<20 ng/mL). We meta-analyzed 887 participants (n = 504 with an insufficient level of vitamin D and n = 383 with a deficient level of vitamin D) from five studies (9,12,13,25,28). No statistical difference was found between groups (OR 0.93, 95% CI 0.69−1.24, I2 = 0%, *P*=.61).

Miscarriage rate

Replete level of vitamin D (≥30 ng/mL) versus insufficient or deficient level vitamin D (<30 ng/mL). We meta-analyzed a total of 881 pregnancies (n = 219 with a replete level of vitamin D and n = 662 with an insufficient or deficient level of vitamin D) from six studies (9,12,13,25,27,28). No difference between comparators was found (OR 1.15, 95% CI 0.72−1.84, I2 = 0%, *P*=.55) (Supplemental Fig. 2).

Replete or insufficient level of vitamin D (≥20 ng/mL) versus deficient level of vitamin D (<20 ng/mL). We meta-analyzed a total of 1087 pregnancies (n = 630 with an adequate or insufficient level of vitamin D, and n = 457 with a deficient level of vitamin D) from eight studies (9,12,13,18,24-26,28). No difference between comparators was found (OR 1.05, 95% CI 0.74−1.51, I2 = 0%, *P*=.78) (Supplemental Fig. 3).

Replete level of vitamin D (≥30 ng/mL) versus insufficient level of vitamin D (<30 ng/mL and ≥20 ng/mL). We analyzed a total of 553 pregnancies (n = 241 with an adequate level of vitamin D and n = 312 with an insufficient level of vitamin D) from five studies (9,12,13,25,28). No difference between comparators was found (OR 0.71, 95% CI 0.44−1.16, I2 = 0%, *P*=.17).

Replete level of vitamin D (≥30 ng/mL) versus deficient level of vitamin D (<20 ng/mL). We analyzed 428 pregnancies (n = 187 with a replete and n = 241 with a deficient level of vitamin D) from five studies (9,12,13,25,28). No statistical difference between groups was found (OR 0.94, 95% CI 0.49−1.80, I2 = 0%, *P*=.86).

Insufficient level of vitamin D (<30 ng/mL and ≥20 ng/mL) versus deficient level of vitamin D (<20 ng/mL). We meta-analyzed 553 pregnancies (n = 312 with an insufficient level of vitamin D and n = 241 with a deficient level of vitamin D) from five studies (9,12,13,25,28). No statistical difference between groups was found (OR 0.71, 95% CI 0.44−1.16, I2 = 0%, *P*=.17).

Ongoing pregnancy/live birth rate

Replete level of vitamin D (≥30 ng/mL) versus insufficient or deficient level of vitamin D (<30 ng/mL. We meta-analyzed a total of 1659 participants (n = 385 with a replete level of vitamin D and n = 1274 with an insufficient or deficient level of vitamin D) from six studies (9,11-13,25,27,28). The group with a replete level of vitamin D showed higher OPR/LBR (OR 0.72, 95% CI 0.53−0.97, I2 = 29%, *P*=.03) (Fig. 2A).

Replete or insufficient level of vitamin D (≥20 ng/mL) versus deficient level of vitamin D (<20 ng/mL). We included a total of 2,712 participants (n = 1,379 with a replete or insufficient level of vitamin D, and n = 1,333 with a deficient level of vitamin D) from nine studies (9,12,13,18,24-26,28,29). No difference between comparators was found (OR 0.89, 95% CI 0.69−1.15, I2 = 49%, *P*=.38) (Fig. 2B).

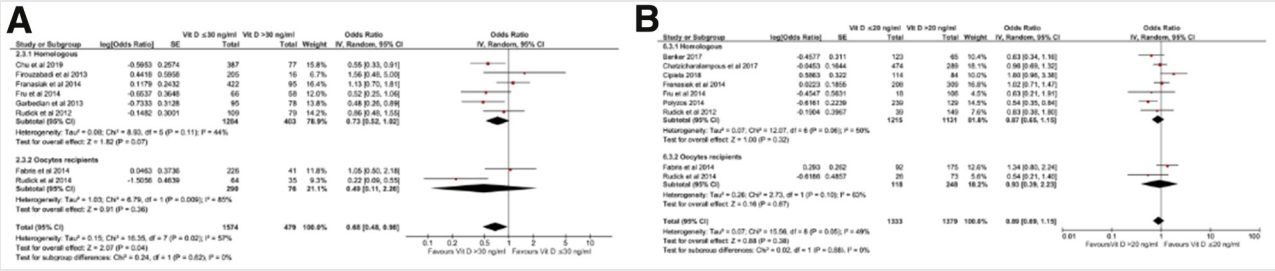
Replete level of vitamin D (≥30 ng/mL) versus insufficient level of vitamin D (<30 ng/mL and ≥20 ng/mL). We included a total number of 812 participants (n = 308 with a replete and n = 504 with an insufficient level of vitamin D) from five studies (9,12,13,25,28). No difference between comparators was found (OR 0.80, 95% CI 0.59−1.08, I2 = 0%, *P*=.15).

Replete level of vitamin D (≥30 ng/mL) versus deficient level of vitamin D (<20 ng/mL). We meta-analyzed 691 participants (n = 308 with a replete and n = 383 with a deficient level of vitamin D) from five studies (9,12,13,25,28). No statistical difference between groups was found (OR 0.82, 95% CI 0.55, 1.21, I2 = 20%, *P*=.32).

Insufficient level of vitamin D (<30 ng/mL and ≥20 ng/mL) versus deficient level of vitamin D (<20 ng/mL). We meta-analyzed 821 participants (n = 504 with an insufficient level of vitamin D and n = 383 with a deficient level of vitamin D) from five studies (9,12,13,25,28). No statistical difference between groups was found (OR 1.07, 95% CI 0.81−1.42, I2 = 0%, *P*=.63).

Subgroup analysis. According to the type of IVF cycle (i.e., homologous and egg donation IVF cycles), subgroup analyses failed to show subgroup differences in terms of the influence

FIGURE 2



Ongoing pregnancy/live birth rate. (**A**) Replete levels of vitamin D (≥30 ng/mL) versus insufficient or deficient levels of vitamin D (<30 ng/mL). (**B**) Replete or insufficient levels of vitamin D (≥20 ng/mL) versus deficient levels of vitamin D (<20 ng/mL).

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of vitamin D levels on primary and secondary outcomes (Figs. 1 and 2).

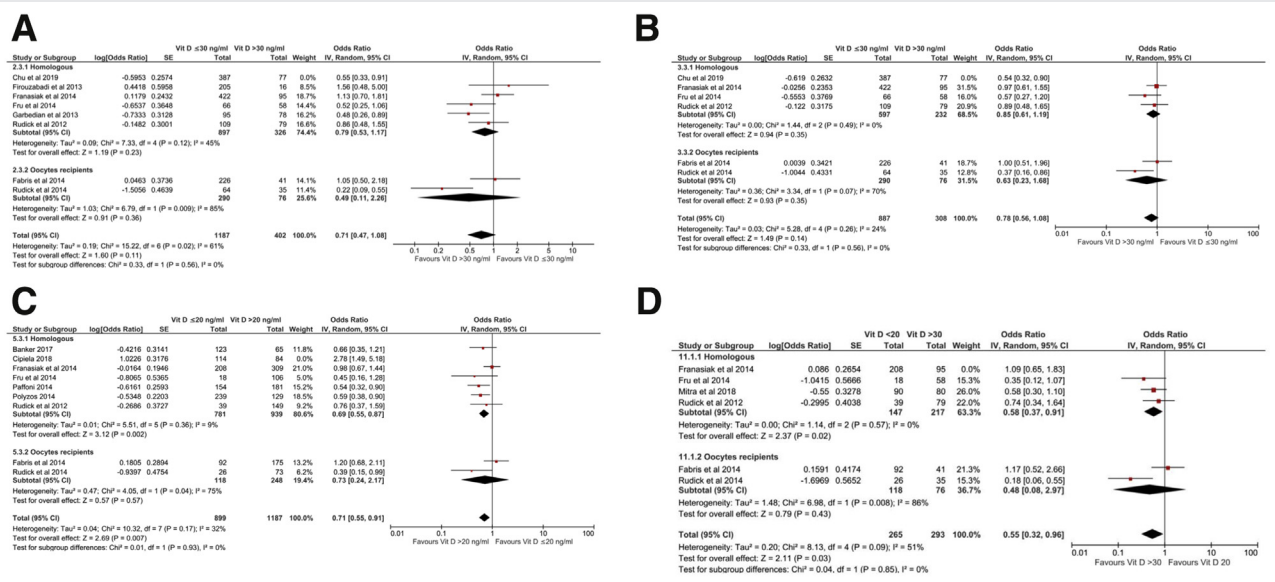
Sensitivity analysis

Replete level of vitamin D (≥ 30 ng/mL) versus insufficient or deficient level of vitamin D (<30 ng/mL). The exclusion of the study by Chu et al. (27) led to a nonsignificant difference between groups for the CPR (OR 0.71, 95% CI 0.47−1.08], I2 = 61%, *P*=.11) and OPR/LBR (OR 0.78, 95% CI 0.56−1.08, I2 = 61%, *P*=.11) outcomes (Figs. 3A and B). The results for the MR outcome were unchanged (data not shown).

Replete or insufficient level of vitamin D (≥ 20 ng/mL) versus deficient level of vitamin D (<20 ng/mL). The exclusion of the study by Ciepiela et al. (24) led to a significant advantage for patients with a level of vitamin D ≥20 ng/mL in terms of CPR (OR 0.71, 95% CI 0.55−0.91, I2 = 32%, *P*=.007) (Fig. 3C). Nevertheless, it did not show this advantage in terms of OPR/LBR and MR (data not shown).

Replete level of vitamin D (≥ 30 ng/mL) versus the insufficient level of vitamin D (<30 ng/mL and ≥ 20 ng/mL). According to methodological quality scores, the serial exclusion

FIGURE 3



(**A**, **B**) Sensitivity analysis on replete levels of vitamin D (≥30 ng/mL) versus insufficient or deficient vitamin D (<30 ng/mL). Exclusion of the study by Chu et al. (27) led to a nonsignificant difference between groups for the clinical pregnancy rate and the ongoing pregnancy/live birth rate. (**C**) Sensitivity analysis on replete or insufficient levels of vitamin D (≥20 ng/mL) versus deficient levels of vitamin D (<20 ng/mL). The exclusion of the study by Ciepiela et al. (24) resulted in a significant advantage in terms of the clinical pregnancy rate, but not in terms of ongoing pregnancy/live birth rate. (**D**) Sensitivity analysis on replete levels of vitamin D (≥30 ng/mL) versus deficient levels of vitamin D (<20 ng/mL). Exclusion of the study by Franasiak et al. (13) resulted in a significant advantage in terms of the clinical pregnancy rate, but not in terms of the ongoing pregnancy/live birth rate.

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of each study or specific study subgroups did not significantly change our results for CPR, MR and OPR/LBR (data not shown).

Replete level of vitamin D (≥30 ng/mL) versus deficient level of vitamin D (<20 ng/mL). The exclusion of the study by Franasiak et al. led to a significant advantage for patients with vitamin D ≥30 ng/mL in terms of CPR (OR 0.55, 95% CI 0.32−0.96, I2 = 51%, *P*=.03) (Fig. 3D). Nevertheless, it did not show this advantage in terms of OPR/LBR and MR (data not shown).

Insufficient level of vitamin D (<30 ng/mL and ≥20 ng/mL) versus deficient level of vitamin D (<20 ng/mL). According to methodological quality scores, the serial exclusion of each study or specific study subgroups did not significantly change our results for CPR MR and OPR/LBR (data not shown).

DISCUSSION

This meta-analysis and systematic review, which included data from 14 studies, found inconsistent evidence supporting a possible impact of vitamin D serum levels on the outcome of IVF cycles. The primary analysis showed higher CPR and OPR/LBR in women with a replete level of vitamin D compared to those with a deficient or insufficient level of vitamin D. However, the sensitivity analysis (considering the exclusion of the study by Chu et al. [27]) showed non-significant differences between comparators (*P*>.05). In the meta-analysis of observational studies, a sensitivity analysis plays a crucial role in demonstrating the trustworthiness of the pooled point estimate (30). Nevertheless, the results of the sensitivity analysis demonstrated that the primary analysis could lead to confusion. Consequently, we could not draw scientifically meaningful causal conclusions regarding vitamin D levels and IVF outcome, despite the observed point estimate. Similarly, the other comparisons (insufficient versus deficient levels of vitamin D; replete versus insufficient levels of vitamin D; replete versus deficient levels of vitamin D; replete or insufficient versus deficient levels of vitamin D) failed to demonstrate a significant difference between groups for the outcomes of CPR, MR, and OPR/LBR. The sensitivity analysis was an important feature in the analysis of the observational studies. In fact, the exclusion of the study by Franasiak et al. also resulted in a significant advantage for patients with vitamin D ≥30 ng/mL in terms of CPR, although not in terms of OPR/LBR and MR. In this case, the exclusion was considered because the interval between vitamin D assessment and frozen embryo transfer in the study was never clearly stated in the manuscript, which leads to possible misclassification biases. According to the study protocol, the patient's vitamin D status was determined on the day of the ovulation trigger. Nevertheless, the authors included fresh and frozen embryo transfer in the analysis, without specifying a time reference when the frozen embryo transfer was performed. Furthermore, all patients included in the study underwent a euploid, blastocyst transfer. However, this paradigm of transfers may not be representative of the regimens of all infertility patients' treatment. In addition, the exclusion of the study by Ciepiela et al. (24) resulted in a significant advantage for patients with vitamin D ≥20 ng/mL in terms of CPR, although not in terms of OPR/LBR and MR. Therefore, there were two reasons for the exclusion: on one hand, the study had a small number of embryo transfers; on the other hand, the generalization of results seemed unlikely because of the strict inclusion criteria.

According to the largest study on this topic, our findings showed a nonsignificant influence of serum vitamin D levels on IVF outcome (31). The largest study on this specific topic could not be included in our meta-analysis for statistical reasons (i.e., data reported in vitamin D quartiles). In their recent study, Jiang et al. (31) analyzed the vitamin D levels in a total of 1,883 women and 1,720 men undergoing IVF. They identified no association between patients' vitamin D levels and embryo development, as well as with clinical outcomes including CPR, MR, and LBR (31).

Our findings update and revise several of the most recent meta-analyses on this topic. In particular, the review by Chu et al. considered fewer studies compared to the present one (i.e., 11 vs. 14) (32). Likewise, it did not comprise several secondary analyses, the function of which would be to assess the strength of causal evidence between vitamin D levels and IVF outcomes.

After a thorough review, Iliuta et al. (33) found some apparent mistakes in the data retrieval from the references of the meta-analysis by Chu et al., as well as in its classification process. In addition, the authors included data from the study by Anifandis et al. (16) in their meta-analysis; however, we excluded this study because it was conducted by testing follicular fluid vitamin D levels. Thus, data from studies on serum vitamin D testing, combined with those on follicular fluid vitamin D testing, might have resulted in a biased point estimate in the study by Chu et al. (32).

The debate over the role of vitamin D in reproductive health is ongoing. Many investigations have focused on the role of vitamin D in terms of overall outcomes. On the other hand, other studies have attempted to parse the role of vitamin D in folliculogenesis, oogenesis, and endometrial receptivity in murine models. Interestingly, Yoshizawa et al. (5) observed major damage in folliculogenesis and underdevelopment of the uterus in knock-out mice with blocked vitamin D receptor genes. Even if vitamin D has an equivalent role in humans, the threshold of vitamin D affecting the reproductive process may be extremely low, presumably lower than 20 ng/mL (i.e., the cut-off below which patients are universally considered to be at a deficient level of vitamin D). Other authors demonstrated that vitamin D plays an important role in influencing the expression of insulin-like growth factor-binding protein−1 (34). In addition, vitamin D is also a key factor in the ovary and specific genes involved in ovarian steroidogenesis. Concerning this aspect, calcitriol was found to enhance the in vitro production of progesterone, estradiol, and estrone by human ovarian cells (35). On this basis, there was speculation that vitamin D, through increased estradiol production (11), might positively influence the number and quality of oocytes retrieved after controlled ovarian stimulation (and consequently IVF success). However, this was not supported by later studies, in which vitamin D serum levels were not correlated with the number and quality of

oocytes retrieved. Farzadi et al. (36) found that follicular fluid (FF) concentrations of vitamin D at the time of oocyte retrieval were significantly higher in women who were pregnant compared to those who were not. Thus, higher vitamin D level in the FF could be related with higher oocyte quality. Another unsolved question is whether vitamin D may influence endometrial receptivity. The expression of osteopontin (a progesterone-regulated adhesion molecule that mediates implantation and decidualization) increased in endometrial cells in response to calcitriol (37). Likewise, calcitriol has been shown to regulate HOXA10 expression in human endometrial stromal cells (38). These findings might support the role that vitamin D plays in endometrial receptivity. Nevertheless, knowledge about the effects of this molecule in the physiological endometrium is still poor, and the molecular mechanisms involved are still to be completely defined.

Most of the favorable IVF treatment outcomes are associated with 25(OH)D thresholds >30 ng/mL. Consequently, vitamin D could be involved in the mechanisms of conception. Examples of these may be uterine receptivity and implantation through endometrial gene expression, or extravillous trophoblast invasion (39). This evidence highlights the importance of vitamin D during preconception and implantation windows. Therefore, we assume that vitamin D has a role in the mechanisms of infertility. Nevertheless, much remains to be learned regarding how vitamin D influences IVF outcomes. The ideal 25(OH)D level for the reproductive function is still unknown, and it may be higher than the existing clinical recommendations. Vitamin D intake recommendations may be higher for women who are trying to conceive or are undergoing fertility treatment than for bone health care (1,40). Hence, this suggests that the next critical steps should be focused on the 25(OH)D dose-response in association with reproductive end goals. The core of our meta-analysis has analyzed several 25(OH)D cut-offs to characterize vitamin D status by evaluating its correlation with relevant IVF outcomes.

Our meta-analysis is not without some limitations. First, we found heterogeneity among the studies included in the meta-analysis, with regard to the dosage of the vitamin D (i.e., before IVF treatment, during ovarian stimulation, or at the time of oocyte retrieval). This must be mentioned as a potential source of bias in our results, although a recent study found that individual vitamin D concentrations remained stable during IVF cycles (41). Second, vitamin D levels in women underwent seasonal physiological fluctuations. Serum levels of vitamin D increased during the summer and autumn months, whereas they decreased during the winter and spring months. This was clearly shown by two studies that examined circulating vitamin D in Australian adolescents (42) and Swedish adults (43). In this case, the recruitment of patients was not performed during the same seasons within studies, potentially limiting the ability to draw firm conclusions. Finally, ethnic heterogeneity among studies in our meta-analysis should be taken into account. In different studies, black or Asian women were found to have lower serum vitamin D levels compared to women of other ethnic groups (44). Therefore, the reference cut-off insufficiency and deficiency levels in vitamin D may need further diversification for each specific ethnic group, which was not possible in this study.

In conclusion, the evidence from this meta-analysis supports that vitamin D serum levels do not seem to be associated with successful IVF reproductive outcomes. Nevertheless, threshold 25(OH)D values >30 ng/mL are related to favorable IVF treatment outcomes, assuming that vitamin D could play a role in the mechanism(s) of infertility. Moreover, the pooled primary analysis on live births showed that serum vitamin D is associated with the live birth rate. In addition, we cannot exclude that the ideal 25(OH)D level for reproductive function could be higher than the actual clinical recommendations. Thus, based on available data, vitamin D serum levels assessed before IVF cycles should not be considered as a prognostic factor for IVF success. Nevertheless, much remains to be known regarding the role of vitamin D in the field of reproductive medicine, as well as which vitamin D cut-offs should be considered. Future large cohort studies are warranted to determine whether the threshold of vitamin D affecting the reproductive process is extremely low compared to those used for bone health care and whether it ultimately varies among different ethnic groups.

REFERENCES

1. Macdonald HM, Mavroeidi A, Aucott LA, Diffey BL, Fraser WD, Ormerod AD, et al. Skin color change in Caucasian postmenopausal women predicts summer-winter change in 25-hydroxyvitamin D: findings from the ANSAViD cohort study. J Clin Endocrinol Metab 2011;96:1677–86.
2. Holick MF. Optimal vitamin D status for the prevention and treatment of osteoporosis. Drugs Aging 2007;24:1017–29.
3. Lerchbaum E, Rabe T. Vitamin D and female fertility. Curr Opin Obstet Gynecol 2014;26:145–50.
4. Cozzolino M. Is it realistic to consider vitamin D as a follicular and serum marker of human oocyte quality? J Assist Reprod Genet 2019;36:173–4.
5. Yoshizawa T, Handa Y, Uematsu Y, Takeda S, Sekine K, Yoshihara Y, et al. Mice lacking the vitamin D receptor exhibit impaired bone formation, uterine hypoplasia and growth retardation after weaning. Nat Genet 1997;16:391–6.
6. Dennis NA, Houghton LA, Jones GT, van Rij AM, Morgan K, McLennan IS. The level of serum anti-Mullerian hormone correlates with vitamin D status in men and women but not in boys. J Clin Endocrinol Metab 2012;97:2450–5.
7. Merhi ZO, Seifer DB, Weedon J, Adeyemi O, Holman S, Anastos K, et al. Circulating vitamin D correlates with serum antimullerian hormone levels in late-reproductive-aged women: Women's Interagency HIV Study. Fertil Steril 2012;98:228–34.
8. Ozkan S, Jindal S, Greenseid K, Shu J, Zeitlian G, Hickmon C, et al. Replete vitamin D stores predict reproductive success following in vitro fertilization. Fertil Steril 2010;94:1314–9.
9. Rudick B, Ingles S, Chung K, Stanczyk F, Paulson R, Bendikson K. Characterizing the influence of vitamin D levels on IVF outcomes. Hum Reprod 2012;27:3321–7.
10. Aleyasin A, Hosseini MA, Mahdavi A, Safdarian L, Fallahi P, Mohajeri MR, et al. Predictive value of the level of vitamin D in follicular fluid on the outcome of assisted reproductive technology. Eur J Obstet Gynecol Reprod Biol 2011;159:132–7.
11. Firouzabadi RD, Rahmani E, Rahsepar M, Firouzabadi MM. Value of follicular fluid vitamin D in predicting the pregnancy rate in an IVF program. Arch Gynecol Obstet 2014;289:201–6.
12. Fabris A, Pacheco A, Cruz M, Puente JM, Fatemi H, Garcia-Velasco JA. Impact of circulating levels of total and bioavailable serum vitamin D on pregnancy rate in egg donation recipients. Fertil Steril 2014;102:1608–12.
13. Franasiak JM, Wang X, Molinaro TA, Green K, Sun W, Werner MD, et al. Free vitamin D does not vary through the follicular phase of the menstrual cycle. Endocrine 2016;53:322–6.

14. van de Vijver A, Drakopoulos P, Van Landuyt L, Vaiarelli A, Blockeel C, Santos-Ribeiro S, et al. Vitamin D deficiency and pregnancy rates following frozen-thawed embryo transfer: a prospective cohort study. Hum Reprod 2016;31:1749–54.
15. Neville G, Martyn F, Kilbane M, O'Riordan M, Wingfield M, McKenna M, et al. Vitamin D status and fertility outcomes during winter among couples undergoing in vitro fertilization/intracytoplasmic sperm injection. Int J Gynaecol Obstet 2016;135:172–6.
16. Anifandis GM, Dafopoulos K, Messini CI, Chalvatzas N, Liakos N, Pournaras S, et al. Prognostic value of follicular fluid 25-OH vitamin D and glucose levels in the IVF outcome. Reprod Biol Endocrinol 2010;8:91.
17. Garbedian K, Boggild M, Moody J, Liu KE. Effect of vitamin D status on clinical pregnancy rates following in vitro fertilization. CMAJ Open 2013;1:E77–82.
18. Polyzos NP, Anckaert E, Guzman L, Schiettecatte J, Van Landuyt L, Camus M, et al. Vitamin D deficiency and pregnancy rates in women undergoing single embryo, blastocyst stage, transfer (SET) for IVF/ICSI. Hum Reprod 2014;29:2032–40.
19. Paffoni A, Ferrari S, Vigano P, Pagliardini L, Papaleo E, Candiani M, et al. Vitamin D deficiency and infertility: insights from in vitro fertilization cycles. J Clin Endocrinol Metab 2014;99:E2372–6.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.
21. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions. Chichester: John Wiley & Sons: 2nd ed; 2019.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
23. Deeks JJ, Hopewell S, Moher D, Higgins JP, Moons KG, Chandler J, et al. Doug Altman's legacy to Cochrane and evidence synthesis. Cochrane Database Syst Rev 2018;8:ED000127.
24. Ciepiela P, Duleba AJ, Kowaleczko E, Chelstowski K, Kurzawa R. Vitamin D as a follicular marker of human oocyte quality and a serum marker of in vitro fertilization outcome. J Assist Reprod Genet 2018;35:1265–76.
25. Rudick BJ, Ingles SA, Chung K, Stanczyk FZ, Paulson RJ, Bendikson KA. Influence of vitamin D levels on in vitro fertilization outcomes in donor-recipient cycles. Fertil Steril 2014;101:447–52.
26. Banker M, Sorathiya D, Shah S. Vitamin D deficiency does not influence reproductive outcomes of IVF-ICSI: a study of oocyte donors and recipients. J Hum Reprod Sci 2020;10:79–85.
27. 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.
28. Fru KH, Segal T, Cox JM, Mumford SL, Sharara FI, Segars JH. Replete vitamin D levels are associated with higher pregnancy rates and increased number of live births in autologous IVF cycles. Fertil Steril 2014;102:e277.
29. Chatzicharalampous C, Saketos M, Sung L, Stelling J, Jackman J, Bray MA. Vitamin D levels and IVF outcomes in women of different ethnic groups. Fertil Steril 2017;108:e118.
30. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167:268–74.
31. Jiang L, Ji L, Song J, Qian K. The effect of serum vitamin D levels in couples on embryo development and clinical outcomes. Reprod Biomed Online 2019;38:699–710.
32. 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.
33. Iliuta F, Pijoan JI, Matorras R. Is the association of replete status in vitamin D with better results in IVF demonstrated? Hum Reprod 2018;33:1797.
34. Parikh G, Varadinova M, Suwandhi P, Araki T, Rosenwaks Z, Poretsky L, et al. Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells. Horm Metab Res 2010;42:754–7.
35. Bakhshalizadeh S, Amidi F, Alleyassin A, Soleimani M, Shirazi R, Shabani Nashtaei M. Modulation of steroidogenesis by vitamin D3 in granulosa cells of the mouse model of polycystic ovarian syndrome. Syst Biol Reprod Med 2017;63:150–61.
36. Farzadi L, Khayatzadeh Bidgoli H, Ghojazadeh M, Bahrami Z, Fattahi A, Latifi Z, et al. Correlation between follicular fluid 25-OH vitamin D and assisted reproductive outcomes. Iran J Reprod Med 2015;13:361–6.
37. Vigano P, Lattuada D, Mangioni S, Ermellino L, Vignali M, Caporizzo E, et al. Cycling and early pregnant endometrium as a site of regulated expression of the vitamin D system. J Mol Endocrinol 2006;36:415–24.
38. Du H, Daftary GS, Lalwani SI, Taylor HS. Direct regulation of HOXA10 by 1,25-(OH)2D3 in human myelomonocytic cells and human endometrial stromal cells. Mol Endocrinol 2005;19:2222–33.
39. Jukic AMZ, Baird DD, Weinberg CR, Wilcox AJ, McConnaughey DR, Steiner AZ. Pre-conception 25-hydroxyvitamin D (25(OH)D) and fecundability. Hum Reprod 2019;34:2163–72.
40. Jukic AMZ, Harmon QE. Accumulating evidence for vitamin D and conception. Fertil Steril 2020;113:330–1.
41. Anagnostis P, Karras S, Goulis DG. Vitamin D in human reproduction: a narrative review. Int J Clin Pract 2013;67:225–35.
42. Mills NT, Wright MJ, Henders AK, Eyles DW, Baune BT, McGrath JJ, et al. Heritability of transforming growth factor-beta1 and tumor necrosis factor-receptor type 1 expression and vitamin D levels in healthy adolescent twins. Twin Res Hum Genet 2015;18:28–35.
43. Snellman G, Melhus H, Gedeborg R, Olofsson S, Wolk A, Pedersen NL, et al. Seasonal genetic influence on serum 25-hydroxyvitamin D levels: a twin study. PLoS One 2009;4:e7747.
44. Mitchell BL, Zhu G, Medland SE, Renteria ME, Eyles DW, Grasby KL, et al. Half the genetic variance in vitamin D concentration is shared with skin colour and sun exposure genes. Behav Genet 2019;49:386–98.

Cómo influyen los noveles de vitamina Den los resultados de fecundación in vitro: resultados de una revisión sistemática y metaanálisis.

Objetivo: investigar el impacto de los niveles séricos de vitamina D en los resultados de fecundación in vitro (FIV).

Diseño: Revisión sistemática y metaanálisis.

Pacientes: mujeres infértiles que se someten a una fecundación in vitro convencional FIV o inyección intracitoplasmática de espermatozoides (ICSI).

Intervenciones: Búsqueda sistemática de PubMed, MEDLINE, EMBASE, Global Health, The Cochrane Library, Health Technology Assesment Database, and Web of Science desde su inicio hasta julio de 2019 con revisión cruzada de referencias de artículos relevantes en inglés. Los niveles de vitamina D fueron categorizados en tres grupos: deficientes (<20ng/mL), insuficientes (20-20ng/mL) y altos (>30ng/mL). Antes de empezar con la recogida de datos, registramos este protocolo de revisión en PROSPERO (CRD42019134258).

Medidas de Resultado Principal: Consideramos la tasa de gestación clínica (TGC), la tasa de recién nacido vico (TRNV) y/o tasa de gestación evolutiva (TGE) como resultados primarios. La tasa de abortos fue considerada un resultado secundario.

Resultados: El análisis primario mostró que las mujeres con un nivel alto de vitamina D sérica tienen TCG, TRNV y TGE más altas comparadas con las mujeres con niveles deficientes o insuficientes. Sin embargo, el análisis de sensibilidad reflejó diferencias no significativas entre los grupos comparados en cuanto a TGC (odds ratio 0.71, 95% intervalo de confianza 0.47-1.08, I2=61%) y TGE/TRNV (odds ratio 0.78, 95% intervalo de confianza 0.56-1.08, I2=61%). Tampoco se encontró diferencia estadísticamente significativa en la tasa de abortos.

Conclusión: Los niveles séricos de vitamina D no influyen sobre los resultados de IVF en términos de TGC, TRNV/TGE, y tasa de aborto. Se justifican futuros amplios de cohortes para determinar si el valor umbral de vitamina D afecta a los resultados reproductivos. Actualmente, no hay consenso sobre los límites apropiados de vitamina D para predecir los resultados reproductivos comparados con los establecidos para la salud ósea.