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Effect of and the association between vitamin D and outcomes of assisted reproductive techniques among infertile men and women: protocol for an overview of systematic reviews and meta-analysis

Bahar Morshed-Behbahani,1 Leila Doryanizadeh 2, Shadab Shahali 3, Saeed Shahabi,4 Ali Montazeri 5

ABSTRACT

Introduction Vitamin D is associated with many functions of the human reproductive system. Accordingly, it seems that on infertile couples undergoing assisted reproduction technology (ART), treatment outcomes may be affected by the vitamin D. This overview aims to show the effect of vitamin D on infertility treatments outcomes in recent studies by concluding systematic reviews and meta-analyses to achieve a comprehensive result.

Methods and analysis This overview protocol is being reported according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) statement and was registered in the International Prospective Register of Systematic Reviews. We will include all peer-reviewed systematic reviews and meta-analyses of randomised controlled trials published from inception until December 2022. PubMed, Web of Science, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects, Scopus, Cochrane Central Register of Controlled Trials and Embase will be searched from the time of publication of the first articles onwards with a comprehensive search strategy. Endnote X7 software (Thomson Reuters, New York, New York, USA) will be used to store and manage records. The results will align with guidelines in the Cochrane Handbook of Systematic Reviews of Interventions and the PRISMA statement.

Ethics and dissemination This overview will be evaluating the effect of vitamin D status and vitamin D supplementing on results of ART in women and men who are undergoing treatment for infertility. The high prevalence of vitamin D deficiency worldwide and its effects on an important issue such as human fertility might be a very influential factor that leads scientists to strongly recommend its use. However, the more critical concern is that there is no definitive agreement in studies on the relationship between vitamin D and an increased chance of better fertility in men and women undergoing infertility treatment.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This article is a well-designed study to provide evidences about the effect of vitamin D on clinical outcomes of infertility.
⇒ This study is an overview of systematic reviews and meta-analysis that enhances the value of study.
⇒ In this study, both the effect of vitamin D status and the effect of vitamin D supplementation have been investigated.
⇒ Our limitation is that the number of studies conducted on infertile men and women is unequal.

BACKGROUND

Acquiring evidence from studies proposes that vitamin D is associated with many functions of the human reproductive system.1 Currently, studies have demonstrated that vitamin D affects the nuclear receptors of vitamin D in the hypothalamic–ovarian–uterine–placental axis that involve producing hydroxylation enzymes to adjust uterine endometrium function in women. This regulation will help to decidualisation the endometrium for better implantation and proper trophoblast function. Also, it is essential for endometrial development.1–3 Likewise, calcitriol (an activated form of vitamin D in the liver and kidneys) is effective in controlling the secretion of human placenta lactogen, oestrogen and progesterone.4 In vitro studies suggest that 1α,25-dihydroxy vitamin D3 improved ovarian follicle survival and growth.5 Furthermore, a controversial relationship is showed between vitamin D and anti-Mullerian hormone in different conditions of ovulatory status and the benefit of vitamin D to female reproduction in general.6 Many studies

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suggested the role of vitamin D in the male reproductive system. Recently, a systematic review study showed a potential beneficial action of vitamin D on male reproductive health, notably through better sperm motility and higher pregnancy rates. However, researchers observed controversy between vitamin D status and testis hormone production.7

Accordingly, it seems that on infertile couples undergoing assisted reproduction technology (ART), treatment outcomes may be affected by the vitamin D. Some studies have suggested an association between vitamin D and reproductive treatment outcomes achieved in women undergoing ART. Their results showed that vitamin D deficiency or insufficiency could be important conditions to treat in women considering ARTs.8 On the other hand, some studies state that vitamin D levels are reliable predictors of ART outcomes is still controversial, and evidence is still poor because no randomised controlled trials (RCTs) are currently available, and results of existing small cohort studies are very heterogeneous.9

This overview aims to show the effect of vitamin D on infertility treatments outcomes in recent studies by concluding systematic reviews and meta-analyses to achieve a comprehensive result. The overview also will assess reviews that report on association between vitamin D and outcomes of infertility treatment. We used the Population, Intervention, Comparison and Outcome (PICO) framework (table 1).

The PICO framework helps us define the research questions.
1. How does vitamin D affect the results of ART?
2. What effect does vitamin D supplement administration have on infertility treatment outcomes?

### METHODS

#### Protocol and registration

This overview protocol is being reported according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) statement and the manuscript is based on the PRISMA-P checklist, which is attached in online supplemental file 1.10 It was registered in the International Prospective Register of Systematic Reviews (PROSPERO). The actual start date was December 2021 and the anticipated completion date will be January 2023.

#### Eligibility criteria

We will include all peer-reviewed systematic reviews and meta-analyses of RCTs published from inception until December 2022. To use the largest range of relevant evidence and compare the best estimates of effectiveness of different trials, we will focus on systematic reviews rather than original experiments. The studies which evaluate the association between vitamin D statuses and assisted reproductive techniques outcomes (semen quality, live birth rates, biochemical pregnancy rates and clinical pregnancy rates) in treated men and women will be included. Each type of ART (In vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and frozen embryo transfer11) will be considered. Whether vitamin D is measured in serum or follicular fluid, the study will have inclusion criteria. Studies of various designs (eg, RCTs and observational studies) will only be included in reviews if the RCT data are reported in separate subgroups. If numerous reviews of the same intervention and patient population are available, we will use the most current Cochrane review unless a more recently published review of comparable quality includes new studies. If there was not a Cochrane review, the most recently published review will be chosen. We will examine all studies thoroughly to make sure we are analysing and reporting the most up-to-date research.

There is a possibility that two or more reviews of the same intervention and patient population will be published in a short period of time (less than 2 years), but with contradictory findings, such as one indicating a considerable drop in admissions and the other showing no benefit. In these circumstances, we will look at the complete texts of the reviews and the list of studies that were included to see how they compare and contrast. In these cases, we will compare and contrast the full texts of the reviews and research lists that were included.

#### Literature sources and search methods

PubMed, Web of Science, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects, Scopus, Cochrane Central Register of Controlled Trials and Embase will be searched from the time of publication of the first articles onwards with a comprehensive search strategy (online supplemental file 2). As well as, we will search the reference lists or bibliographies of included studies. We will search the common registry databases such as ClinicalTrials.gov, PROSPERO, Center for Open Science and WHO International Clinical Trials Registry Platform. Only English literature will be searched and entered to the study. First, the search strings (online supplemental file 2) will be written and developed for PubMed database, and after that we will adapt it for other electronic databases. The research team will consider three components of PICO including Intervention, Outcome and Study Design during search strategy development. For having a comprehensive search, we will look

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The PICO framework to define the research question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Women and men under infertility treatment</td>
</tr>
<tr>
<td>Intervention</td>
<td>Vitamin D prescription/observe vitamin D status among samples with successful treatment</td>
</tr>
<tr>
<td>Comparators</td>
<td>No vitamin D prescription/observe vitamin D status among samples with failed treatment</td>
</tr>
<tr>
<td>Outcome</td>
<td>Semen quality, pregnancy (chemical/clinical)</td>
</tr>
</tbody>
</table>

**PICO, population, intervention, comparison and outcome.**
for MeSH and Emtree thesauruses to recruit appropriate terms. Also, free-text approach and contacting with relevant expert will be applied to find more relevant terms.

**Screening and study selection procedure**
Endnote V.X7 software (Thomson Reuters, New York, New York, USA) will be used to store and manage records. Following removal of duplicates, titles and abstracts will be screened against the eligibility criteria by two independent reviewers (LD, SS), and full-text papers will be collected for all titles that meet the inclusion criteria or for which eligibility is unclear. This step will also be conducted by two reviewers independently. A third reviewer will be invited to settle any disputes about study inclusion. Where two studies found to be duplicated, the most recent and complete edition will be chosen and included.

**Data extraction**
A data extraction tool is available as online supplemental file 3.

The main data that will be extracted by two reviewers are: author(s) name, year of publication, search duration of study, databases that used, final included studies (number) or total participants (number) that included, participants’ characteristics (age, sex, type of studies), source of vitamin D sample or vitamin D supplement, vitamin D grouping criteria, number of embryos transferred or outcome (chemical or clinical pregnancy or live birth), summary of main results (effect on PCO or endometriosis or quality of sperm or…) or main conclusion, heterogeneity index between studies outcome ($I^2$), effect size ($95\% \text{ CI}$), quality assessment status (number of high quality/low quality), publication bias (yes/no), registration of protocol, funding source and type of heterogeneity of studies (fixed or random model). Any disagreement in this step will be resolved by discussion and participation of third reviewer (BM-B).

**Quality assessment and risk of bias**
The methodological assessment and evaluation of the risk of bias of each study will be assessed by PRISMA guideline and also AMSTAR 2, which is a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Two independent reviewers will be involved in this step, and as in the previous steps, discussion and consulting with third reviewer will be applied to resolve any disagreement. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria will be used to evaluate the final quality of evidence for interested outcomes in eligible studies. To show the GRADE profile of each study, six criteria including: publication bias, imprecision, indirectness, effect size, inconsistency and risk of bias will be employed. Specifically, GRADE results will be described as very low, low, moderate and high which revealing the certainty and strength level of evidence.12 13

**Statistical analysis**
The results will align with guidelines in the Cochrane Handbook of Systematic Reviews of Interventions14 and the PRISMA statement.15 We will be using a PRISMA flow diagram to summarise the study selection, and the characteristics of included reviews will be tabulated in the summary table. Furthermore, any descriptive explanations of heterogeneity provided by the review authors when the $I^2$ is greater than 50% as this may represent substantial heterogeneity will be reported.14 So, the user of the results can give greater consideration to the situations in which the effect estimates are applicable. We will provide hierarchical lists of interventions ranked by consideration of the quality of the evidence, and review AMSTAR score, and give a brief explanation of the studies of heterogeneity.

We will use proportions for dichotomous data and averages with 95% CIs or medians with IQRs for continuous data to summarise the characteristics of the included reviews in tables. The absolute risk difference and the quality of the evidence will be used to rank interventions.

**Patient and public involvement**
Patients and the public were not (or will not be) involved in this overview.

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**Contributors** BM-B supervised the study, the main investigator, designed the study and wrote the first draft. LD provided key information, and contributed to writing process. SSShahal was the study advisor, provided background information. SShahal helped in methodology. AM was the study advisor, critically reviewed the manuscript and provided the final draft. All authors read and approved the manuscript.

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