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Original

Association between serum vitamin D levels and IVF–ICSI outcomes in women with polycystic ovary syndrome: A prospective cohort study

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Abstract

Background: The association between vitamin D status and assisted reproductive technology outcomes remains uncertain, particularly in women with polycystic ovary syndrome (PCOS). This study evaluated the association between serum vitamin D levels and selected laboratory and pregnancy outcomes after vitro fertilization with intracytoplasmic sperm injection (IVF–ICSI) in women with PCOS.

Methods: This prospective cohort study included 128 women with PCOS undergoing IVF–ICSI at Yas Hospital, Tehran, Iran (March 2017–March 2018). Serum vitamin D was measured on the day of oocyte retrieval. were categorized into two groups based on vitamin D levels: insufficient (<30 ng/mL; n = 83) and normal (≥30 ng/m; n = 45). Oocyte, embryo, and pregnancy outcomes were recorded. Analyses included independent-group comparisons and univariate logistic regression.

Results: Mean age was 30.3 ± 3.9 years and mean body mass index (BMI) 24.6 ± 2.8 kg/m². Compared with the insufficient vitamin D group had higher mean numbers of mature (MII) oocytes (p = 0.016), embryos (p = 0.032), and grade A embryos (p = 0.001). Total oocyte count did not differ significantly. Forty participants (31.3%) had a positive chemical pregnancy test and 22 (17.2%) had a clinical pregnancy. Univariate logistic regression showed an association between vitamin D category and chemical pregnancy (p = 0.042).

Conclusion: In women with PCOS undergoing IVF–ICSI, higher serum vitamin D levels were associated with better laboratory outcomes. However, the observational design and limited evidence regarding pregnancy outcomes preclude causal conclusions. Further prospective studies are needed to clarify the role of vitamin D in reproductive outcomes.

Keywords: Fertilization in Vitro, Infertility, Female, Oocytes, Polycystic Ovary Syndrome, Pregnancy Rate, Vitamin D

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Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder during reproductive age and is frequently associated with ovulatory dysfunction and infertility (1) . For women with PCOS who undergo in vitro fertilization with intracytoplasmic sperm injection (IVF–ICSI), treatment outcomes may be influenced by multiple clinical and metabolic factors, including age, body mass index, ovarian response, and embryo development.

Vitamin D has biological functions beyond calcium and bone metabolism (2-4). Vitamin D is metabolized to its active form, and vitamin D receptors and local vitamin D-metabolizing enzymes have been identified in reproductive tissues, including the ovary, uterus, placenta, hypothalamus, and pituitary gland (5-12). These findings provide a plausible biological basis for a relationship between vitamin D status and reproductive processes (13). This potential role in reproductive physiology has also been discussed previously (8). Vitamin D status has also been associated with metabolic characteristics relevant to PCOS, including obesity and insulin resistance (14, 15).

Nevertheless, evidence linking serum vitamin D levels to IVF–ICSI outcomes is inconsistent. Some studies have reported associations with ovarian response, embryo development, or pregnancy outcomes (16, 17), whereas others have found no meaningful relationship or have reported differing associations with embryo quality (15, 17, 18). Differences in study populations, vitamin D measurement, timing of measurement, outcome definitions, and sample size may contribute to these inconsistent findings.

This study therefore examined the association between serum vitamin D levels measured on the day of oocyte retrieval and selected oocyte, embryo, and pregnancy outcomes among women with PCOS undergoing IVF–ICSI.

Materials & Methods

This prospective cohort study was conducted at Yas Hospital in Tehran, Iran, from March 2017 to March 2018. The study included 128 women with PCOS who underwent IVF–ICSI.

Eligible participants were women with PCOS undergoing IVF–ICSI who provided informed consent. Exclusion criteria were failure to complete the IVF process for technical reasons, inability to measure serum vitamin D, or withdrawal of consent.

Serum vitamin D was measured on the day of oocyte retrieval using the study laboratory's standard method. Participants were classified into two groups: serum vitamin D below 30 ng/mL (insufficient vitamin D) and serum vitamin D of at least 30 ng/mL (normal vitamin D). The 30 ng/mL threshold was the study's prespecified classification cut-off.

Demographic and clinical information included age, body mass index (BMI), education, pregnancy history, gravidity, infertility history and duration, miscarriage history, ectopic pregnancy history, underlying conditions, and prior medical procedures. The reported laboratory outcomes included total oocyte count, oocyte maturity categories (GV, MI, and MII), embryo count, number of embryos transferred, and embryo grades (A, B, and C).

Chemical pregnancy was defined as a positive serum β-hCG result 14 days after embryo transfer. Clinical pregnancy was defined as visualization of a gestational sac on transvaginal ultrasonography.

The study was approved by the Institutional Review Board of Tehran University of Medical Sciences (approval code IR.TUMS.MEDICINE.REC.1398.090). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Statistical analysis

Descriptive statistics (mean, standard deviation, relative frequency) were used. Between-group comparisons used the chi-square test for categorical variables and the independent-samples t-test for continuous variables. Univariate logistic regression was used for the association between vitamin D category and chemical pregnancy. Analyses were performed with SPSS version 23; $p < 0.05$ was considered statistically significant.

Results

Of the 128 women, 83 (64.8 %) had insufficient vitamin D and 45 (35.2 %) had normal vitamin D. Mean age was 30.3 ± 3.9 years and mean BMI was 24.6 ± 2.8 kg/m². Primary infertility was reported by 114 participants (89.1 %); 28 (21.8 %) had a history of miscarriage and 10 (7.8 %) had a history of ectopic pregnancy. Mean age, BMI, and duration of infertility did not differ significantly between groups (Table 1).

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Table 1. Demographic and clinical characteristics by serum vitamin D category (n = 128)

Variable	Insufficient Vitamin D (n=83) Mean ± SD	Normal Vitamin D (n=45) Mean ± SD	p-value
Mean women age (years)	30.0 ± 4.0	30.8 ± 3.6	0.25
Mean women BMI (km/m^2)	24.5 ± 2.8	24.7 ± 2.9	0.73
Mean infertility duration (years)	4.0 ± 2.4	3.2 ± 1.8	0.07

Note: BMI; body mass index

Mean total oocyte count did not differ significantly (9.1 ± 3.8 vs 10.2 ± 4.4; p = 0.143). The mean number of MII oocytes was higher in the normal vitamin D group (5.2 ± 2.7 vs 3.9 ± 2.9; p = 0.016). Mean embryo count (6.2 ± 3.0 vs 5.1 ± 2.7; p = 0.032) and mean number of grade A embryos (2.3 ± 1.4 vs 1.4 ± 1.2; p = 0.001) were also higher in the normal vitamin D group. No significant between-group differences were observed in the numbers of grade B or grade C embryos or the number of embryos transferred (Table 2).

Table 2. The para clinical history of the women separately for the two groups of patients (n = 128)

Variable	Insufficient Vitamin D (n=83) Mean ± SD	Normal Vitamin D (n=45) Mean ± SD	p-value
Mean oocyte number	9.1 ± 3.8	10.2 ± 4.43	0.143
Mean oocyte quality			
GV	2.3 ± 2.0	2.37 ± 2.1	0.738
MI	2.9 ± 1.7	2.7 ± 2.1	0.462
MII	3.93 ± 2.9	5.2 ± 2.7	0.016
Mean embryos number	5.1 ± 2.7	6.2 ± 3.0	0.032
Mean fetus transfer	1.3 ± 0.5	1.1 ± 0.3	0.053
Mean embryos quality			
A	1.4 ± 1.2	2.3 ± 1.4	0.001
B	2.2 ± 1.5	2.3 ± 1.5	0.801
C	1.5 ± 1.7	1.6 ± 1.3	0.682

Note: GV; germinal vesicle, MI, metaphase I, MII; metaphase II

As shown in Figures 1 and 2, 40 of 128 participants (31.3%) had a positive chemical pregnancy test, and 22 (17.2%) achieved a clinical pregnancy. Univariate logistic regression revealed a statistically significant association between serum vitamin D category and chemical pregnancy (p = 0.042), whereas no statistically significant association was observed with clinical pregnancy.

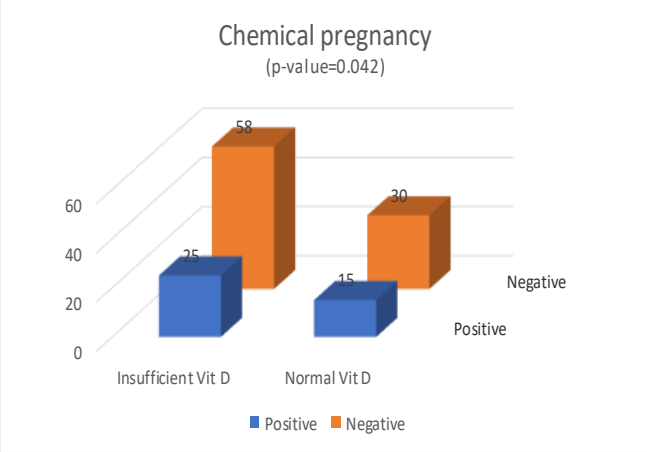


Figure 1 Frequency distribution of chemical pregnancy results in two groups of patients

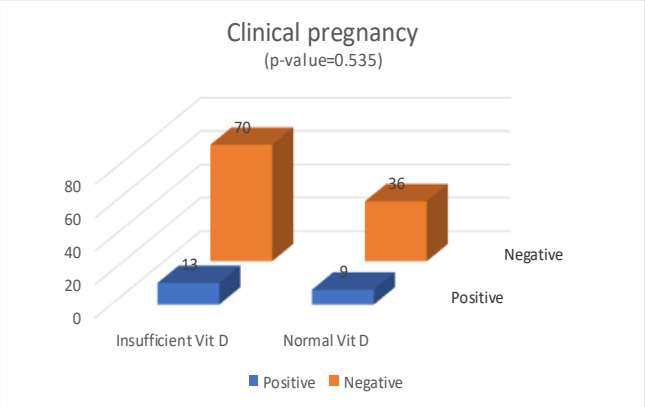


Figure 2 Frequency distribution of clinical pregnancy results in two groups of patients

Discussion

In this cohort of women with PCOS undergoing IVF–ICSI, serum vitamin D levels of at normal vitamin D group were associated with a higher mean number of mature MII oocytes, a higher reported embryo count, and a higher mean number of grade A embryos. Total oocyte count did not differ significantly between groups. The pregnancy findings are less certain because the manuscript provides inconsistent descriptions of the chemical pregnancy analysis and

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does not report the group-specific event counts or effect estimates.

The association between vitamin D status and selected laboratory outcomes is biologically plausible, given the presence of vitamin D receptors and vitamin D-metabolizing enzymes in reproductive tissues (7-11). Vitamin D status may also be related to metabolic characteristics relevant to PCOS, including obesity and insulin resistance (14, 15). However, biological plausibility does not establish causation. Vitamin D status may also reflect other characteristics, including body composition, metabolic health, diet, sun exposure, season, or general health. These factors may influence ovarian response or be associated with treatment outcomes independently of vitamin D.

The findings should be interpreted alongside the mixed evidence on vitamin D and assisted reproduction. Previous studies have reported both positive associations and no clear associations between vitamin D status and IVF outcomes (16-18). Other studies have examined ovarian stimulation outcomes in women with PCOS and other infertility populations (19, 20). Studies have also reported associations between vitamin D and fertility outcomes across different IVF populations (17-19). Differences across studies may arise from variation in participant characteristics, assay methods, the timing of vitamin D measurement, thresholds used to classify vitamin D status, stimulation protocols, embryo grading systems, and definitions of pregnancy outcomes. The present study measured vitamin D on the day of oocyte retrieval; therefore, it does not establish whether vitamin D status before ovarian stimulation has the same relationship with outcomes.

The higher mean number of MII oocytes and grade A embryos in the group with vitamin D levels of at least 30 ng/mL should not be interpreted as evidence that vitamin D supplementation would improve IVF success. Previous research has examined vitamin D in relation to embryo development, fertilization, and reproductive outcomes, with findings that are not fully consistent (16-18, 21). Vitamin D was observed rather than assigned, and the reported analyses do not adequately control for potential confounding. In addition, the study did not report live birth, the most clinically definitive reproductive outcome. The number of embryos, embryo grade, biochemical pregnancy, and clinical pregnancy are intermediate outcomes and do not necessarily translate into higher live-birth rates.

Previous studies have reported inconsistent findings regarding the association between vitamin D status and reproductive outcomes in women with PCOS undergoing assisted reproductive treatment. Pal et al. investigated vitamin D status in relation to reproductive outcomes in women with PCOS (22), whereas Luo et al. found no significant associations between serum vitamin D levels and embryo quality or pregnancy outcomes (23). Similarly, Tian et al. reported weak or no meaningful associations between vitamin D measures and functional fertility parameters in women undergoing IVF/ICSI (24). These discrepancies suggest that the relationship between vitamin D status and reproductive outcomes remains inconclusive (22-24).

Other studies have addressed related but distinct research questions. Ko et al. examined the association between serum vitamin D levels measured before ovarian stimulation and cumulative live birth following IVF (25), while Meng et al. evaluated the effects of vitamin D supplementation on reproductive outcomes through a systematic review and meta-analysis (26). However, these findings address different exposures and outcomes and should be interpreted in their respective contexts. The present observational study evaluated vitamin D status in relation to laboratory and pregnancy outcomes in women with PCOS undergoing IVF/ICSI; it did not assess vitamin D supplementation or live birth. Therefore, its findings cannot establish whether supplementation improves IVF outcomes or whether vitamin D status predicts cumulative live birth.

Several limitations should be acknowledged. First, the study was conducted at a single center and included only 128 participants, which limits precision and generalizability. Second, vitamin D was measured on the day of oocyte retrieval, so the study cannot determine whether earlier vitamin D status or changes during treatment are associated with outcomes. Third, the analyses described are primarily unadjusted, leaving potential confounding by age, BMI, metabolic characteristics, treatment protocol, and other clinical factors. Fourth, multiple laboratory outcomes were tested, increasing the possibility of chance-positive findings. Fifth, the manuscript reports incomplete and inconsistent information about pregnancy outcomes and follow-up. Finally, live birth and cumulative live-birth outcomes were not reported.

Conclusion

In this single-center cohort of women with PCOS undergoing IVF–ICSI, serum vitamin D levels of ≥30 ng/mL were associated with higher mean numbers of

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mature oocytes and grade A embryos, as well as a higher embryo count. Although vitamin D category was significantly associated with chemical pregnancy in univariate logistic regression, this finding should be interpreted cautiously, and no significant association with clinical pregnancy was observed. Given the observational design, these findings do not establish causality or demonstrate that vitamin D supplementation improves reproductive outcomes. Further prospective studies with appropriate confounder adjustment, prespecified reproductive endpoints, and follow-up to live birth are needed to clarify the role of vitamin D in IVF–ICSI outcomes.

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Conflicts of Interest

The authors declare no conflict of interest.

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