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Original Research Article

Vitamin D supplementation in infertile women with PCOS: a quasi-randomized placebo-controlled study

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder associated with infertility and metabolic dysfunction. Vitamin D deficiency is prevalent in women with PCOS and may exacerbate hormonal and metabolic derangements. This study evaluated the effects of vitamin D supplementation on ovulatory and metabolic outcomes across PCOS phenotypes in a placebo-controlled setting.
Methods: In this 24-month quasi-randomized placebo-controlled trial, 180 infertile women with PCOS (Rotterdam criteria) and serum 25(OH)D <20 ng/mL were randomly allocated to Group A (n = 90, received cholecalciferol 60,1 IU/week for 9 weeks) or Group B (n = 90, received placebo capsules identical in appearance and schedule). Allocation was based on alternate patient recruitment. Both groups were stratified into four PCOS phenotypes. Clinical, biochemical, and ultrasonographic parameters were assessed. Multivariable regression adjusted for BMI, WHR, season, and ethnicity. Effect sizes (β) and 95% confidence intervals (CI) were reported.
Results: After 9 weeks, Group A showed a significant rise in 25(OH)D levels (mean 28.7±7.6 ng/mL) versus Group B (13.4±5.5 ng/mL, p<1.2). Ovulation occurred in 35/90 (38.10%) in Group A and 17/90 (18.10%) in Group B (p = 1.2). Adjusted regression showed reductions in LH: FSH ratio (β = -1.28; 95% CI: -1.51 to -1.6), total testosterone (β = -7.4; 95% CI: -12.10 to -1.7), and HOMA-IR (β = -1.53; 95% CI: -1.82 to -1.24). HDL levels increased (β = +1.13 mmol/L; 95% CI: 1.5 to 1.21). Phenotype A showed the highest ovulatory response (45.6% vs 20.9%; p = 1.3).
Conclusions: Vitamin D supplementation significantly improved ovulatory and metabolic parameters in vitamin D-deficient infertile women with PCOS, especially in hyperandrogenic phenotypes. Phenotype-tailored vitamin D therapy may serve as an effective adjunct in PCOS management

Keywords: FSH ratio, Infertility, Insulin resistance, Ovulation, PCOS, Phenotypes, Placebo-controlled, Vitamin D

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous endocrine disorder affecting approximately 9-13% of women of reproductive age worldwide. It manifests through a combination of clinical and/or biochemical hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (PCOM), as defined by the Rotterdam criteria.[1] These features not only contribute to infertility but also predispose affected women to long-term metabolic complications, including insulin resistance and dyslipidemia.[2]

Recent research has suggested a potential role of vitamin D in female reproductive health.[3] Beyond its classical function in calcium and bone metabolism, vitamin D has been implicated in modulating insulin sensitivity, ovarian folliculogenesis, and sex hormone production. Several studies have reported a high prevalence of vitamin D deficiency in women with PCOS, with associations linking

low serum 25-hydroxyvitamin D [25(OH)D] to increased insulin resistance, hyperandrogenism, and anovulation.[2]

Despite these associations, interventional studies on vitamin D supplementation in PCOS have yielded inconsistent results, potentially due to variations in study design, population characteristics, and the phenotypic heterogeneity of PCOS.[3] Some phenotypes may exhibit differential responses to vitamin D therapy based on the degree of metabolic and hormonal dysregulation.

This study aimed to evaluate the effect of vitamin D supplementation on ovulatory function and metabolic parameters in infertile, vitamin D-deficient women with polycystic ovary syndrome (PCOS), stratified by phenotype.

METHODS

Study design and setting

This quasi-randomized, placebo-controlled trial was conducted from June 2022 to September 2023 in the Department of Reproductive Endocrinology at MLB Medical College, Jhansi, a tertiary care center in Uttar Pradesh, India. Ethical approval was obtained from the Institutional Ethics Committee (Ref No: IEC/MLB/2022/8). Written informed consent was obtained from all participants. The quasi-randomization method used was alternate allocation at enrollment. The participants and outcome assessors were blinded to group assignments.

A total of 180 infertile women aged 20-40 years were recruited. PCOS was diagnosed using the Rotterdam criteria, and only those with serum 25(OH)D levels <20 ng/mL were included. Infertility was defined as failure to conceive after at least 13 months of unprotected intercourse.[3]

Inclusion criteria included women aged between 20-40 years, diagnosed with PCOS based on at least two of the following: hyperandrogenism, oligo/anovulation, and polycystic ovarian morphology (PCOM), with serum 25(OH)D <20 ng/mL, and at least one year of infertility.4Diagnosis of PCOS based on at least two of the following: hyperandrogenism, oligo/anovulation, PCOM, Serum 25(OH)D <20 ng/mL. At least one year of infertility.

Exclusion criteria included other causes of infertility, such as tubal blockage or male factor infertility; presence of endocrine disorders, including thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, or Cushing's syndrome; recent use (within 4 months) of vitamin D or hormonal therapy; and any severe systemic illness. Other causes of infertility (e.g., tubal blockage, male factor infertility), Endocrine disorders (thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, Cushing's syndrome), use of vitamin D or hormonal therapy within the last 4 months, Severe systemic illness

Intervention and grouping participants were alternately allocated into two groups: Group A (n=90): received oral cholecalciferol 60,1 IU once weekly for 9 weeks, Group B (n=90): received identical-looking placebo capsules on the same schedule.

Participants were further classified into PCOS phenotypes based on the Rotterdam criteria: Phenotype A: Hyperandrogenism + Ovulatory Dysfunction + PCOM; Phenotype B: Hyperandrogenism + Ovulatory Dysfunction; Phenotype C: Hyperandrogenism + PCOM; Phenotype D: Ovulatory Dysfunction + PCOM.

Assessments

Data collection included menstrual history, BMI, waist-to-hip ratio (WHR), and clinical signs of hyperandrogenism (modified Ferriman-Gallwey score). Blood samples were obtained during the early follicular phase (days 3-6 of the cycle) or randomly in amenorrheic women. Laboratory tests measured serum 25(OH)D, LH, FSH, total testosterone, fasting glucose, and insulin; HOMA-IR was calculated. Transvaginal ultrasound was used for antral follicle count (AFC), ovarian volume, and ovulation tracking via folliculometry and mid-luteal serum progesterone.

Statistical analysis

Statistical analysis was performed using SPSS version 25. Descriptive statistics were expressed as mean±SD or median (IQR) for continuous variables, and frequency (percentage) for categorical variables. Comparisons between groups used an independent samples t-test or Mann-Whitney U test for continuous variables, and a chi-square test for categorical variables. Multivariable linear and logistic regression models were applied to assess the independent effect of vitamin D supplementation on outcomes, adjusting for BMI, WHR, season, and ethnicity. A p value <1.6 was considered statistically significant.

RESULTS

Baseline characteristics

The demographic, anthropometric, and biochemical parameters of participants are summarized in Table 1. No statistically significant differences were observed between Group A and Group B at baseline concerning age, BMI, WHR, serum 25(OH)D, HOMA-IR, LH: FSH ratio, and total testosterone, confirming initial homogeneity.

Serum 25(OH)D levels and ovulatory response

Following 9 weeks of intervention, serum 25(OH)D levels significantly increased in Group A (mean±SD: 28.7±7.6 ng/mL) compared to Group B (13.4±5.5 ng/mL; p<1.2).

Ovulation was observed in 35 women (38.10%) in the intervention group versus 17 women (18.10%) in the placebo group (p = 1.2), indicating a statistically significant improvement in ovulatory function (Table 2).

Table 1: Baseline characteristics of participants.

Parameter	Group A (n=90)	Group B (n=90)	P value
Age (years)	28.3±4.1	28.5±4.2	0.72
BMI (kg/m²)	27.6±3.7	28.0±4.1	0.48
WHR	0.85±0.05	0.86±0.06	0.55
Serum 25(OH)D (ng/ml)	12.1±4.6	11.9±4.2	0.75
HOMA-IR	2.54±0.9	2.58±0.8	0.62
LH: FSH ratio	1.8±0.6	1.9±0.7	0.68
Total testosterone (ng/dl)	55.2±15.3	54.8±14.9	0.88

Table 2: Post-intervention outcomes.

Parameter	Group A (n=90)	Group B (n=90)	P value
Serum 25(OH)D (ng/ml)	28.6±6.5	12.3±4.4	<0.001
Ovulation rate (%)	38.9	18.9	0.01
LH: FSH ratio	1.4±0.5	1.8±0.6	0.03
Total testosterone (ng/dl)	48.9±13.2	54.2±14.7	0.04
HOMA-IR	2.01±0.7	2.54±0.8	<0.01
HDL (mmol/l)	1.35±0.3	1.23±0.4	0.04
Triglycerides (mmol/l)	1.45±0.5	1.63±0.6	0.09

Hormonal and metabolic outcomes

Significant reductions in the LH: FSH ratio (from 2.5±1.6 to 2.1±1.6, p = 1.2) and serum total testosterone (from 55.3±15.4 to 48.10±13.3 ng/dL, p = 1.5) were observed in the supplemented group (Table 3). Additionally, HOMA-IR decreased significantly from 3.54±1.9 to 3.2±1.8 (p<1.2), indicating improved insulin sensitivity. HDL cholesterol levels increased significantly from 2.23±1.5 to 2.35±1.4 mmol/L (p = 1.5). Triglyceride levels showed a non-significant reduction.

Phenotype-specific ovulation response

When stratified by PCOS phenotypes, Group A exhibited higher ovulation rates across all phenotypes, with the most marked response in hyperandrogenic phenotypes. Phenotype A showed a significant difference in ovulation rates between intervention and placebo groups (45.6% vs. 20.9%; p = 1.3). Phenotype B also showed a significant improvement (36.5% vs. 16.8%; p = 1.5). Improvements in phenotypes C and D were not statistically significant (Table 3).

Table 3: Phenotype-specific ovulation rates.

PCOS phenotype	Group A (%)	Group B (%)	P value
Phenotype A	45.5	20.8	0.02
Phenotype B	36.4	16.7	0.04
Phenotype C	31.8	18.2	0.09
Phenotype D	27.3	16.7	0.12

Phenotype-specific responses

Table 3 details the differential response based on PCOS phenotypes. Women with hyperandrogenic phenotypes (A and B) demonstrated significantly higher ovulation rates following supplementation (Phenotype A: 45.6% vs. 20.9%, p = 1.3; Phenotype B: 36.5% vs. 16.8%, p = 1.5). These phenotypes also exhibited more notable hormonal and metabolic improvements compared to non-hyperandrogenic phenotypes, indicating phenotype-specific responsiveness to vitamin D therapy (Table 3).

Multivariable regression analysis

Multivariable regression analysis adjusting for BMI, WHR, season, and ethnicity confirmed the independent association of vitamin D supplementation with favorable outcomes (Table 4). There were significant reductions in LH: FSH ratio (β = -1.28, 95% CI: -1.51 to -1.6; p = 1.4), total testosterone (β = –7.4, 95% CI:-12.10 to -1.7; p = 1.5), and HOMA-IR (β = -1.53, 95% CI: -1.82 to -1.24; p<1.2). HDL levels increased significantly (β = +1.13, 95% CI: 1.5 to 1.21; p = 1.5), while triglyceride change did not reach statistical significance (β = -1.18, 95% CI: -1.39 to 1.4; p = 1.10).

Table 5: Multivariable regression analysis of post-treatment outcomes.

Outcome parameter	β Coefficient	95% Confidence interval	P value
LH: FSH Ratio	-0.28	-0.51 to -0.05	0.03
Total testoste-rone (ng/dL)	-6.3	-11.9 to -0.6	0.04
HOMA-IR	-0.53	-0.82 to -0.24	<0.01
HDL (mmol/L)	+0.12	0.04 to 0.21	0.04
Triglycerides (mmol/L)	-0.18	-0.39 to 0.03	0.09

DISCUSSION

This study investigated the effects of vitamin D supplementation on hormonal, metabolic, and ovulatory parameters in infertile women with polycystic ovary syndrome (PCOS) across different phenotypes. Our findings demonstrate that vitamin D supplementation significantly increased serum 25(OH)D levels, which correlated inversely with key hyperandrogenic markers,

including the LH: FSH ratio and serum testosterone reported by Holick et al. Furthermore, supplementation led to improved ovulation rates, enhanced lipid profiles, and reduced insulin resistance, particularly in hyperandrogenic phenotypes.

Vitamin D and hormonal regulation

The inverse relationship observed between serum 25(OH)D and the LH: FSH ratio is consistent with previous studies suggesting that vitamin D influences gonadotropin secretion and ovarian steroidogenesis.[10] Pal et al reported that vitamin D modulates LH secretion and reduces hyperandrogenemia in women with PCOS, findings that align with our results. Additionally, vitamin D's role in suppressing androgen production may be mediated through its action on ovarian theca cells, which express vitamin D receptors (VDR), as demonstrated by Asadipooya et al. Our results further support the hypothesis that correcting vitamin D deficiency can ameliorate hyperandrogenism, a key contributor to anovulation and clinical symptoms in PCOS.[6,11]

Ovulation and reproductive outcomes

The significant increase in ovulation rates following vitamin D supplementation, especially among hyperandrogenic phenotypes, corroborates prior research emphasizing vitamin D's role in folliculogenesis. Yang et al observed higher ovulation and conception rates in PCOS women who received vitamin D supplementation, paralleling our findings. This suggests that optimizing vitamin D status may help restore ovarian function, potentially by improving granulosa cell health and follicular synchronization.[12]

Metabolic improvements

Our observed reductions in insulin resistance and increases in HDL cholesterol after vitamin D intervention are in agreement with meta-analyses by Lim et al, which concluded that vitamin D supplementation can improve insulin sensitivity and lipid profiles in women with PCOS. The mechanisms underlying these benefits may involve vitamin D's effects on insulin receptor expression and the reduction of inflammation, both of which are relevant to the pathogenesis of metabolic syndrome in PCOS. These findings reinforce the growing consensus that vitamin D has multidimensional benefits extending beyond reproductive health.[13]

Phenotype-specific responses

Notably, hyperandrogenic phenotypes (A and B) exhibited more pronounced improvements compared to phenotypes C and D.[13] This heterogeneity in response underscores the importance of individualized treatment approaches. Phenotypic variations influence the degree of hormonal and metabolic disturbances, and our data suggest that women with hyperandrogenic features may derive greater benefit from vitamin D therapy, as also indicated by Krul-Poel et al.

While promising, our study has several limitations. The relatively short duration of supplementation (9 weeks) restricts the assessment of long-term reproductive and metabolic outcomes. Additionally, confounding factors such as sun exposure, dietary intake, and physical activity were not rigorously controlled and may have influenced vitamin D status and metabolic parameters. Larger, multicenter trials with extended follow-up are warranted to validate these findings and clarify the long-term benefits of vitamin D supplementation in PCOS.

CONCLUSION

Vitamin D supplementation effectively elevates serum 25(OH)D levels and improves endocrine and metabolic parameters in women with PCOS. The most pronounced benefits are observed in hyperandrogenic phenotypes, underscoring the importance of phenotypic stratification in personalized management approaches.

Recommendations

Our findings reinforce the potential role of vitamin D as an adjunct therapy in the management of PCOS, especially for women with hyperandrogenism and vitamin D deficiency. Future research should explore optimal dosing strategies, long-term effects on fertility, and mechanistic pathways, including VDR polymorphisms and intraovarian vitamin D metabolism.

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