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**Title page**

Title: **Prevalence of vitamin D deficiency in infertile women with polycystic ovarian syndrome and its association with metabolic syndrome – A prospective observational study**

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## Condensation

The current study found a high prevalence of vitamin D deficiency in infertile PCOS women and no association was found between metabolic syndrome and hypovitaminosis D.


## Abstract:

**Objective:** The main purpose of this study was to determine the prevalence of vitamin D deficiency in infertile women with polycystic ovarian syndrome (PCOS) and to explore the association of hypovitaminosis D with metabolic syndrome in women with PCOS.

**Study design:** A prospective observational study was conducted in a tertiary care, infertility centre from March 2016 to March 2017. The primary outcome was estimation of the prevalence of vitamin D deficiency in infertile PCOS women. Secondary outcomes were to study the association of hypovitaminosis D with metabolic syndrome, obesity and hypercholesterolemia in PCOS patients.

**Results:** A total of 256 infertile women with PCOS were included in the study**.**Vitamin D deficiency was observed in 70.3 % women, 20.3 % were vitamin D insufficient and only 9.4 % were vitamin D sufficient. Metabolic syndrome was seen in 80/256 (31.25%) women. There was no evidence of an association between hypovitaminosis D and metabolic syndrome, obesity or hyperlipidemia. There was a strong evidence of an association between waist circumference of > 80 cm and vitamin D deficiency ($p$= 0.02).

**Conclusion:** Vitamin D deficiency is highly prevalent in infertile PCOS women and there seems to be no association between hypovitaminosis D and the metabolic syndrome in the same population.

**Key words:** polycystic ovarian syndrome, vitamin D, hypovitaminosis D

**Introduction:**

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of the reproductive age group. Worldwide, the prevalence of PCOS varies from 2.2 % to 26 % [1-5**].** The prevalence of PCOS depends upon the criteria used for diagnosis. In a meta analysis by Ding T [6], Chinese women had the lowest prevalence (5.6%) and middle east women (Turkish and Iranian) had the highest prevalence (16%) based on Rotterdam criteria. The clinical features of this disorder include menstrual irregularities, hyperandrogenic features and infertility. It can also be associated with hyperinsulinemia, impaired blood sugars, hypercholesterolemia, hypertension, obesity and metabolic syndrome [7,8,9]. Women with PCOS are at an increased risk for developing Type 2 diabetes mellitus and cardiovascular disease [10,11].

Vitamin D deficiency is a global health burden due to its high prevalence worldwide. An estimated 1 billion people worldwide are vitamin D deficient or insufficient [12]. Middle east and South Asian countries, in spite of having abundant sunlight have the highest rates of vitamin D deficiency [13,14]. The prevalence of vitamin D deficiency in the general population in South Asia is reported to be in the range of 67-82 % [13] and in the middle east around 20-80% [14]. The prevalence of vitamin D deficiency in Caucasians is lower (28.4%) when compared to 77.4% in Asians [15]. Earlier studies have shown an increased prevalence of vitamin D deficiency in PCOS population [16]. However, there is a paucity of data regarding prevalence of vitamin D deficiency in PCOS women from the South Asian population.

Studies have also shown that vitamin D receptor complex regulates genes involved in glucose metabolism, lipid metabolism and blood pressure regulation, thereby suggesting a role of vitamin D deficiency in the pathogenesis of metabolic syndrome [17]. In women with type II diabetes mellitus, there is an association between low levels of vitamin D and

increased insulin resistance [18,19]. Various observational studies have documented an association of low vitamin D levels with obesity, insulin resistance and hypertension in PCOS women [20,21]. Studies have also shown that supplementation with vitamin D in PCOS patients resulted in improved menstrual regularity, restoration of ovulation and reduction in insulin resistance [22].

The prevalence of metabolic syndrome in PCOS women varies according to ethnicity. The reported range varies from 1.6% in Czech women [23] to 43% in American women [24]. Due to such differences in prevalence linked to ethnicity, we planned a study to investigate prevalence of vitamin D deficiency and its association with metabolic syndrome in South Asian PCOS women.

**Methods and methodology:**

This was a prospective observational study conducted on PCOS women in a tertiary level infertility unit in South India between March 2016 and March 2017. The study was approved by an institutional review board and registered under CTRI (REF/2016/08/011984).

Infertile PCOS women in the age group of 20 to 40 years were invited to participate in the study. The diagnosis of PCOS was based on the 2003 Rotterdam consensus [25]. Patients with congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumours, hypothyroidism and intake of any medication affecting endocrine parameters were excluded from the study.

Metabolic syndrome was defined by the Modified American Heart Association/National Heart Lung Blood Institute AHA/NHLBI (ATP III 2005) definition [26]. According to this definition at least three of the following five features should be present (i) Waist circumference of > 88 cm (80 cm for Asians) (ii) Fasting blood glucose of ≥ 100 mg/dl (iii)Triglycerides ≥ 150 mg/dl (iv) HDL < 40 mg/dl (v) Blood pressure > 130/ 85 mm Hg.

Vitamin D deficiency was defined as a serum vitamin D level of <20 ng/ml and insufficiency was defined as values between 20-30 ng/ml. Hypovitaminosis was defined as serum vitamin D levels <30 ng/ml [27].

An informed and written consent was obtained from each participant. A detailed history, including the length of menstrual cycles; personal, medical, and family history of diabetes; hypertension; obesity; and ischemic heart disease were noted. Signs of androgen excess (acne, hirsutism, alopecia) and blood pressure were noted. Blood pressure was measured in sitting position after a 5-min rest using a standard sphygmomanometer. Waist circumference in centimeter (cm) was measured at the narrowest circumference, midway between the lower rib margin and upper border of the iliac crest. Weight was measured in kilogram (kg) and height was recorded in centimeter (cm). Patients were categorized as underweight, normal weight, overweight, obese and morbidly obese based on WHO classification. Underweight was defined as body mass index (BMI) less than 18.5 kg/m$^2$, normal weight as BMI between 18.5- 24.9 kg/m$^2$ ,overweight as BMI between 25.0 and 29.9 kg/m$^2$, obesity as a BMI of $\geq$ 30.0 kg/m$^2$ and morbidly obese as BMI $\geq$40 kg/m$^2$ [28]. Blood investigations included fasting blood sugar, fasting lipid profile, thyroid stimulating hormone levels and serum vitamin D levels. All the women also underwent a pelvic ultrasonography for ovarian morphology.

The laboratory analyses used the following assays to measure the endocrine parameters: TSH was measured by two site sandwich immunoassay (ADVIA Centaur, Bayer Corporation, Tarry town, NY, USA), blood glucose levels by GOD POD – glucose oxidase and peroxidase methods. Total cholesterol was measured via the cholesterol oxidase peroxidase method (CHO-POD). Triglyceride level was measured using the lipase, glycerokinase, glycerol-3-phosphate oxidase and peroxidase method. HDL cholesterol was determined by the cholesterol esterase, oxidase, peroxidase method. Vitamin D was measured by the Chemiluminescence (CLIA) method. The primary outcomes were to study the prevalence of vitamin D deficiency in PCOS women.

Secondary outcomes were to study the association of vitamin D status with metabolic syndrome, obesity and hypercholesterolemia in PCOS women.

**Statistical analysis:**

Normally distributed and skewed variables were presented as Mean±SD and Median (IQR). Categorical data were presented as number and percentage. To compare with and without metabolic syndrome, Parametric *t* test and also non-parametric Mann Whitny test was used as per the normality. The Chi-square test was used to assess the association. The Pearson correlation was used to assess the relationship between BMI and Vitamin D. Simple and multiple logistic regression analyses were performed to examine the associations of metabolic syndrome (outcome) with 25(OH)D, BMI, and age. Analysis was done using Statistical Package for Social Services (SPSS) software Version 21.0 (Armonk, NY: IBM Corp).

**Results:**

A total of 256 PCOS infertile women from South India were included in the study. The prevalence of vitamin D deficiency was 70.3 % (180/256) in the study population of PCOS women. Vitamin D insufficiency was prevalent in 20.3 % (52/256) and only 24/256 (9.4 %) PCOS women had normal levels of vitamin D. Overall, hypovitaminosis D accounted for 90.6 % (232/256) of the study population.

The baseline characteristics of the study population and two groups (with and without metabolic syndrome) are as shown in table 1. Variables such as age, BMI, waist circumference, mean systolic and diastolic pressure, prior history of diabetes mellitus, & hypertensive disorder, mean fasting and postprandial blood sugar levels, TSH, total cholesterol and triglyceride levels were significantly higher whereas HDL levels were significantly lower in women with metabolic syndrome. There was no difference in the vitamin D levels amongst both the groups.

In the current study, metabolic syndrome was seen in 31.25 % (80/256) PCOS women. Vitamin D deficiency was seen in 76.2 % (61/80) amongst those with metabolic

syndrome and 67.6 % (119/176) without it, respectively ($p$= 0.37). Hypovitaminosis D was seen in 92.5 % (74/80) of PCOS women with metabolic syndrome and in 89.8 % (158/176) PCOS women without metabolic syndrome, with no evidence of an association between metabolic syndrome and hypovitaminosis D ($p$=0.49). Additionally, there was no difference when the mean vitamin D values were compared between the two groups. The mean vitamin D level in women with metabolic syndrome was 15.95 ± 8.36 ng/ml and in those without metabolic syndrome was 17.31 ± 8.75 ng/ml ($p$= 0.19).

There was no association when BMI categories and the prevalence of hypovitaminosis D was compared ($p$= 0.54) as shown in table 2. The Pearson correlation test showed a negative correlation (r= 0.12 with $p$=0.06) of vitamin D levels with BMI, again suggesting no evidence to support an association between BMI and hypovitaminosis D (Figure 1).

There was a strong evidence to support that vitamin D levels were lower when the waist circumference was ≥ 80 cm. In women with waist circumference of <80 cm (n=21), the mean vitamin D level was 19.9± 8.6 ng/ml and in women with waist circumference of ≥ 80 cm (n=235), the mean vitamin D level was 16.6± 8.6 ng/ml ($p$= 0.02). There was no evidence to support an association when vitamin D levels were compared with various lipid parameters like hypercholesterolemia ($p$= 0.31), hypertriglyceridemia ($p$= 0.53) low HDL ($p$=0.61) and high LDL ($p$=0.31).

In logistic regression analyses, metabolic syndrome was associated with BMI (odds ratio (OR) 3.77, 95% confidence interval (CI) (1.74, 8.15) and age (OR 1.08), CI (1.00, 1.16) but not with hypovitaminosis D (Table 3).

**Discussion:**

The findings of the current study indicate that the prevalence of vitamin D deficiency in South Asian PCOS women was 70.3 %. There was no increased prevalence of hypovitaminosis D in the subgroup of PCOS women with metabolic syndrome compared to those PCOS women without metabolic syndrome. There was no association of vitamin

D status with BMI or lipid levels. Vitamin D levels were significantly lower in women with waist circumference ≥ 80 cm.

Few earlier studies in PCOS women, which evaluated non-Asian population have found a vitamin D deficiency prevalence ranging from 37 % [29] to 44 % [30] which is lower than current study finding. This could be due to the high prevalence of vitamin D deficiency seen in general population itself in South Asia with prevalence ranging between 44 % to 94.4 % [31, 32, 33]. The high prevalence of vitamin D deficiency has been attributed to poor dietary habits, socioeconomic conditions, malnutrition, certain cultural habits and lack of awareness [34,35].

An observational study by Wehr E et al [36] showed that vitamin D deficiency in Caucasian women with PCOS was 39 % (80/206) and metabolic syndrome was observed in 12.2 % of PCOS women. Amongst women with metabolic syndrome, 72 % were vitamin D deficient, 28 % had vitamin D insufficiency and none were vitamin D sufficient. Vitamin D levels were significantly lower in PCOS women with metabolic syndrome compared to women without metabolic syndrome ($p$= <0.001). The prevalence of vitamin D deficiency was lower and not in agreement with current study findings. This could be attributed to ethnic variation in the PCOS study population. Consequently, metabolic syndrome prevalence was also lower compared to current study results.

In another study from Iran, Rashidi H et al [34] reported 85% prevalence of hypovitaminosis D, which is in agreement with current study results. Further, the authors did not find any association between metabolic syndrome and vitamin D deficiency. This could be attributed to a common underlying factor of high prevalence of vitamin D deficiency in PCOS women similar to study population. Perhaps this resulted in reduced differences between prevalence of vitamin D deficiency in PCOS women with and without metabolic syndrome.

Many observational studies have shown that vitamin D levels had an inverse correlation with insulin resistance, BMI, waist circumference and fat mass [21,30]. Contrary to these

findings, Rashidi H et al [34] observed that vitamin D deficiency was not associated with insulin resistance or hypercholesterolemia .While the current study did find an association of vitamin D levels with waist circumference, no association was found between BMI or lipid levels, which could be again attributed to ethnic differences in prevalence of vitamin D in PCOS population. A systematic review by Krul- Poel YHM et al [35] found an inverse relationship between vitamin D deficiency and the metabolic syndrome in PCOS. However, the author concluded that a definite causal association between metabolic syndrome and vitamin D deficiency cannot be confirmed due to heterogeneity in the studies. The heterogeneity could be due to inclusion of studies involving PCOS women of different ethnicity. Future research should be planned keeping in view the prevalence of vitamin D deficiency in study population and ethnic differences which will help in calculation of appropriate sample size calculation and explore the association with metabolic syndrome. Only once the causal relationship is proved between vitamin D deficiency and the metabolic syndrome in PCOS women, we can evaluate the effect of various interventions such as vitamin D supplements and amelioration of symptoms associated with PCOS.

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**Conclusion:**

In conclusion, the current study found a high prevalence of vitamin D deficiency in infertile PCOS women from South India. No evidence of an association was found between metabolic syndrome and hypovitaminosis D in the current study. Future studies evaluating the association of metabolic syndrome with vitamin D should calculate an appropriate sample size based on ethnic differences in the prevalence of vitamin D.

**Disclosure statement:**

The authors report no conflict of interest.

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**Figure 1: Pearson correlation of Vitamin D status and body mass index (BMI):**

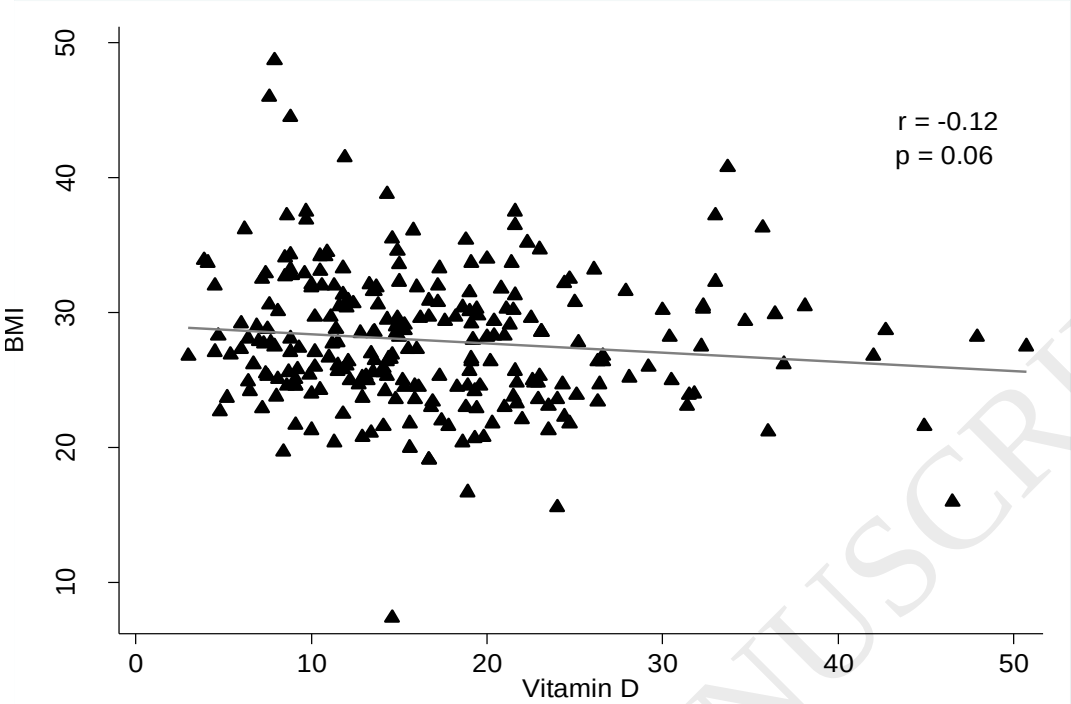

**Table 1: Baseline characteristics of study participants:**

| | All patients (n=256) n(%) | With metabolic syndrome (n=80) n (%) | Without metabolic syndrome (n=176) n (%) | P value |
|---|---|---|---|---|
| Age (years )* | 26.50± 3.98 | 27.55± 3.9 | 26.03±3.93 | 0.004 |
| Type of infertility<br><br>Primary infertility<br><br>Secondary infertility | <br><br>176 (68.8)<br><br>80 (31.3) | <br><br>51 (63.8)<br><br>29 (36.3) | <br><br>125 (71.0)<br><br>51 (29.0) | <br><br>0.24 |
| Prior diabetes mellitus | 10 (3.9) | 8 (10.0) | 2 (1.1) | 0.002 |
| Prior hypertension | 5 (2.0) | 4 (5.0) | 1 (0.6) | 0.034 |
| Prior thyroid disorder | 41 (16.0) | 18 (43.9) | 23 (56.1) | 0.056 |
| BMI* (kg/m2) | 27.9 ±5.05 | 29.92 ±4.95 | 27.03± 4.85 | <0.001 |
| Waist circumference* (cm) | 93.08 ± 11.49 | 98.58±10.91 | 90.58±10.89 | <0.001 |
| Systolic BP* (mm/hg) | 115.73 ± 13.31 | 122.30±15.37 | 112.74±11.08 | <0.001 |
| Diastolic BP*(mm/hg) | 76.61 ± 9.11 | 81.75±10.42 | 74.28±7.36 | <0.001 |
| Fasting blood sugar *(mg/dL) | 98.90 ± 22.58 | 116.28±32.75 | 91.0±7.62 | <0.001 |
| Post prandial blood sugar* (mg/dL) | 115.48 ± 44.63 | 146.16 ± 63.14 | 101.53± 21.82 | <0.001 |
| TSH** (IU/mL) | 2.5 (1.7,3.4) | 2.65 (1.7,3.9) | 2.40 (1.60,3.17) | 0.017 |
| Total Cholesterol (mg/dL) * | 166.90 ± 30.94 | 183.08±31.00 | 159.55±28.05 | <0.001 |

| | | | | |
|---|---|---|---|---|
| Triglycerides (mg/dL)** | 115.50 (79.0,149.75) | 168.0 (130.5,221) | 96.50 (64.0,126.7) | <0.001 |
| HDL (mg/dL)* | 39.78 ±9.47 | 34.34±6.59 | 42.26±9.57 | <0.001 |
| LDL (mg/dL)* | 106.95± 27.20 | 120.0 ±28.68 | 101.01±24.37 | 0.24 |
| Vitamin D (ng/mL)* | 16.89 ± 8.64 | 15.95 ±8.36 | 17.31± 8.75 | 0.236 |

*mean±SD, ** median (inter-quartile range)

BMI= Body mass index, BP= Blood pressure, TSH= Thyroid stimulating hormone, HDL= High density Lipoprotein, LDL= Low density lipoprotein

**Table 2: Association of Vitamin D levels and obesity**

| BMI (kg/m²) | Vitamin D deficiency (n=180) n (%) | Vitamin D insufficiency (n= 52) n (%) | Vitamin D sufficiency (n= 24) n (%) | P value |
|---|---|---|---|---|
| Underweight (<18.5) | 2 (1.1) | 1 (1.9) | 1 (4.2) | 0.54 |
| Normal weight (18.5- 24.9) | 44 (24.4) | 18 (34.6) | 5 (20.8) | |
| Over weight (25-29.9) | 76 (42.2) | 18 (34.6) | 10 (41.7) | |
| Obese (≥ 30) | 54 (30) | 15 (28.8) | 7 (29.2) | |
| Morbidly obese (≥ 40) | 4(2.2) | - | 1(4.2) | |

**Table 3: Association between risk factors of metabolic syndrome using binary and multivariate logistic regression analysis**.

| | Simple Logistic regression | | Multivariate Logistic regression | |
|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| Hypovitaminosis D | 1.41 (0.54,3.69) | 0.49 | - | - |
| BMI (kg/ m²) | 4.29 (2.01,9.17) | <0.0001 | 3.77 (1.74, 8.15) | 0.001 |
| Age (years) | 1.10 (1.03, 1.18) | 0.005 | 1.08 (1.00, 1.16) | 0.043 |

BMI= body mass index

Data presented as odds ratio (OR) and 95% confidence interval (95% CI)