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Research Article

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Vitamin D Deficiency in Infertile Women with Polycystic Ovary Syndrome: A Case-Control Study

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ABSTRACT

Vitamin D deficiency is highly prevalent in women with polycystic ovary syndrome (PCOS). The aim of the study is to compare the prevalence of Vitamin D deficiency and its seasonal variations between PCOS infertile women and other infertile women. A total of 314 infertile women (n= 157) infertile women with PCOS as case and (n=157) infertile women with other infertile woman as control. The patients were attending to the infertility clinic at Imam Khomeini Hospital, Ahvaz, Iran were recruited into this study. Variables were gathered including age, BMI, season of blood sampling, duration of infertility and infertile factors. Women were included as case group if they had infertility due to PCOS (according to Rotterdam criteria), history of infertility, both groups had normal prolactin, normal thyroid function tests, FSH<8.9mlU/ml. Inclusion criteria for control group were infertility due to factors other than PCOS and history of infertility. Exclusion criteria for both case and control groups included were taking medications containing calcium, metformin, OCP, or vitamin D within recent 3 months, uncontrollable diabetes, physiologic or pathologic ovarian cysts, premature ovarian failure syndrome, hypothalamic amenorrhea, endometriosis and smoking. From of all participants were collected 2 cc sample bloods for measurement serum vitamin D.Serum vitamin D concentrations were widely variable in both case and control groups, ranges of 0.5-89 ng/ml and 2.1-100 ng/ml, respectively. The mean serum vitamin D concentration in case group was significantly lower than control group (13±11.5 ng/ml and 25.07±20.7 ng/ml, respectively) (P<0.001). The mean seasonal vitamin D concentrations did not differ in case group (P=0.4), but this was significant in control group (P=0.02). Overall, mean vitamin D levels in all of patients were observed during the autumn more than the other seasons. The majority of studied patients (n=205, 65.3%) had vitamin D deficiency. We found high prevalence and also seasonal variations of vitamin D deficiency women in the south west of Iran. Vitamin D deficiency in infertile PCOS women was more prevalent than the other infertile patients. Therefore, we suggest measuring serum vitamin D especially in infertile PCOS.

Keywords: Serum 25(OH)D, Infertility, Polycystic ovary syndrome

INTRODUCTION

Serum 25-hydroxyvitamin D (25[OH] D) plays an important role in human health, surveillance and reproduction (1). Vitamin D deficiency is highly prevalent in women with polycystic ovary syndrome (PCOS) (2).

Vitamin D level is commonly accepted as the functional indicator for vitamin D status in the body (3). To date, there

is no general agreement on the adequate serum level of vitamin D that is best for health. The concentrations of 25(OH) D are generally classified as follows: levels less than 50 nmol/L (20 ng/mL) are categorized as vitamin D deficiency, 50 to 74 nmol/L (20-30 ng/mL) as insufficiency, and the serum levels higher than 74 nmol/L (30 ng/mL) as adequate (4-11).

PCOS is of the most common endocrine diseases in up to 18% of women of reproductive age (3). Characterizations of PCOS are including polycystic ovaries, menstrual dysfunction, infertility and elevated androgens, acne and hirsutism (3, 5, 12-15). A number of studies have shown associations between PCOS and high incidence of risk factors for cardiovascular disease (CVD) including subclinical atherosclerosis, dyslipidaemia, type II diabetes, and impaired glucose tolerance (6, 7, 16). Obesity and insulin resistance coexist with the development of PCOS and its associated clinical features (8, 17-20). Rising obesity rates suggests the high incidence of PCOS in future. This will potentially decrease population growth and will increase the rate of cardiovascular morbidity and mortality, and consequently, PCOS has become a major public health issue(3). The proportion of 67–85% of women with PCOS having serum concentrations of vitamin D (25OHD) <20 ng/ml (2).It has been suggested that PCOS development is influenced by vitamin D through gene transcription. Also, hormonal changes impact insulin metabolism and fertility regulation (9, 21-24).

There are rare studies evaluating the serum vitamin D level between infertile women with etiology of PCOS and otherwise PCOS. This study aimed to compare and evaluate the prevalence of Vitamin D deficiencyand also its seasonal variations between PCOS infertile women and infertile women with other infertility related diagnoses.

MATERIALS AND METHODS

A total of 314 infertile women attending the infertility clinic at Imam Khomeini Hospital, fertility, infertility and perinatology care research center, in Ahvaz, IRAN from March 2014 to September 2015 were recruited into this study. The study was approved b ethics committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.AC.1394.331). All participants assigned informed consent. Of 314 subjects, 157 infertile women with PCOS were enrolled as “case”, and 157 infertile women with other infertility related diagnoses than PCOS were recruited as “control”. The non-fasting blood samples of studied populations were collected, and then were analyzed by using Elecsys e-411 Cobas (Roche Diagnostics International LTD, Switzerland). The serum vitamin D concentrations were used to determine the vitamin D status as follows: the vitamin D level below 20 ng/ml was defined as deficiency, between 20 and 20 ng/ml as insufficiency and above 30 ng/ml as sufficiency. Patient demographic characteristics and background data were gathered including age, BMI, season of blood sampling, duration of infertility and infertility related diagnoses (male factor, uterine or tubal related infertility and unexplained infertility). Women were included as case group if they had infertility due to PCOS (according to Rotterdam criteria), history of infertility, both groups had normal prolactin, normal thyroid function tests, FSH<8.9mlU/ml. Inclusion criteria for control group were infertility due to factors other than PCOS and history of infertility. Exclusion criteria for both case and control groups included were taking medications containing calcium, metformin, OCP, or vitamin D within recent 3 months, uncontrollable diabetes, physiologic or pathologic ovarian cysts, premature ovarian failure syndrome, hypothalamic amenorrhea, endometriosis and smoking.

The primary outcome of this study was to compare the prevalence of vitamin D deficiency between infertile PCOS women and infertile non-PCOS women. Clinical and biochemical properties between two groups were compared using student t-test and chi square test for continuous and categorical variables, respectively. The results are presented as mean± standard deviation (SD) or absolute frequency (percentage). The multiple logistic regression models with odds ratio was utilized to present the odds of vitamin D deficiency in an infertile woman with PCOS compared to infertile woman without PCOS.

RESULTS

All available infertile patients with measured vitamin D levels between March 2014 and September 2015 participated in this study (case, N=157 and control, N=157). The mean age of case group (28.5 (yr) ±5.2) was significantly lower than control group (30.8 (yr) ±5) (P<0.0001). There was no difference between case and control group on BMI and duration of infertility (P=0.2 and P= 0.7, respectively) (Table 1).

Table 1. Clinical characteristics and some other study parameters

Variable		Group		P value
		Infertile with PCOS	Infertile with other causes	
Age		28.54 ± 5.2	30.84 ± 5.0	<0.0001
BMI (kg/m2)		27.65 ± 3.3	26.78 ± 4.1	0.2
Infertility duration (yr)		4.99 ± 4.8	4.0 ± 5.17	0.7
Frequency of patients at different seasons	Spring	38 (24.2)	41 (26.3)	0.5
	Summer	46 (29.2)	35 (22.4)	
	Autumn	45 (28.2)	48 (30.4)	
	Winter	28 (17.8)	32 (20.5)	
Causes of infertility in control group	Male factor	-	75 (47.7)	
	Male factor and tubal	-	3 (1.9)	
	Tubal	-	14 (8.9)	
	Uterine	-	12 (7.6)	
	Uterine and male factor	-	1 (0.6)	
	Unexplained	-	52 (33.1)	

The distribution of infertile women did not vary between the seasons (P=0.5). The rates of infertility related diagnoses in the control group are presented in Table 1. Of 157 infertile women in the control group, 75 (47.7%) and 52 (32.1%) were with male factor and unexplained infertility. The comparison of vitamin D concentrations between two-study populations are summarized in Table 2.

Table 2. Comparing serum vitamin D concentrations between infertile women with PCOS and infertile women with other causes of infertility

Variable		Group		P value
		Infertile with PCOS	Infertile with other causes	
Serum vitamin D concentration (ng/ml) (min-max)		0.5 - 89	2.1 - 110	
Mean serum vitamin D concentration (mean ± SD)		13 ± 11.5	25.07 ± 20.7	<0.0001
Vitamin D concentration at different seasons (mean ± SD)	Spring	12.82 ± 10.46	21.46 ± 16.38	0.007
	Summer	11.92 ± 8.39	25.30 ± 16.61	<0.001
	Autumn	15.24 ± 11.97	31.12 ± 26.87	<0.001
	Winter	11.64 ± 13.5	18.88 ± 16.25	0.046
Serum vitamin D classification (mean ± SD)	<20 ng/ml	127 (80.8)	78 (49.7)	<0.0001
	20-29 ng/ml	18 (11.5)	37 (23.5)	
	>29 ng/ml	12 (7.6)	42 (26.7)	

Serum vitamin D concentrations were widely variable in both case and control groups, ranges of 0.5-89 ng/ml and 2.1-100 ng/ml, respectively. The mean serum vitamin D concentration in PCOS patients was significantly lower than non-PCOS infertile patients (13±11.5 ng/ml and 25.07±20.7 ng/ml, respectively) (P<0.001). The mean seasonal vitamin D concentrations (using ANOVA test) did not differ in PCOS patients group (P=0.4), but this was significant in non-PCOS infertile women (P=0.02). Overall, the mean vitamin D levels were more during the autumn more than the other seasons (Figure 1).

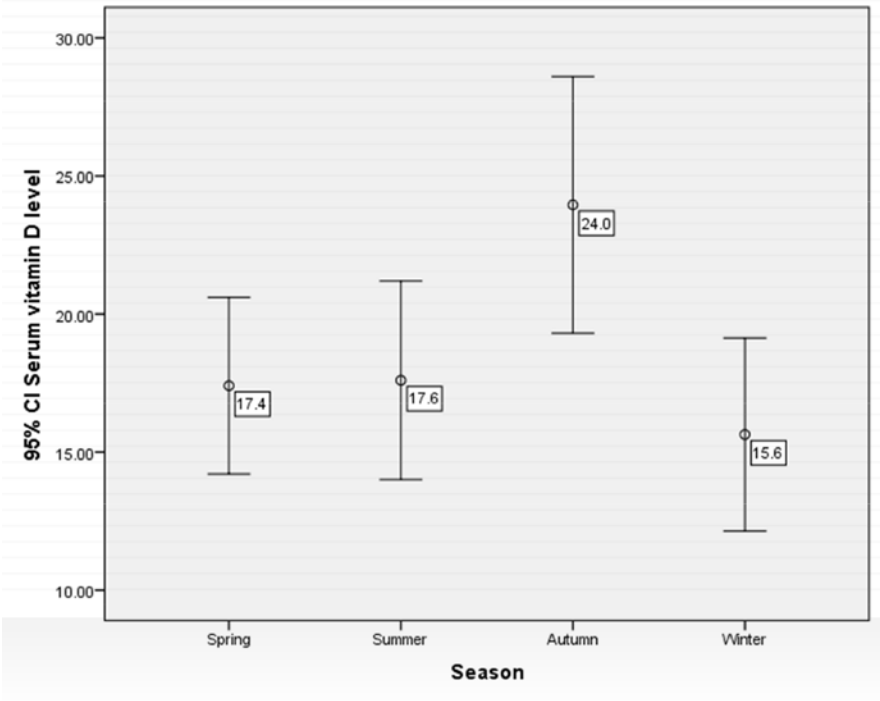

Figure 1. Comparing mean serum vitamin D concentrations between four trimesters of year

The majority of all of patients (n=205, 65.3%) had vitamin D deficiency. Of those, 127 (80.8%) subjects were infertile PCOS and 78 (49.7%) were infertile with other reasons than PCOS. Of 314 patients of studied sample, 55 (17.5%) and 54 (17.2%) were found to be vitamin D insufficient and sufficient, respectively. The proportion of PCOS women with different levels of vitamin D (deficiency, insufficiency and sufficiency) was significantly higher than this proportion in non-PCOs women; this difference mostly related to deficiency category (P<0.001, chi square test)(Figure 2).

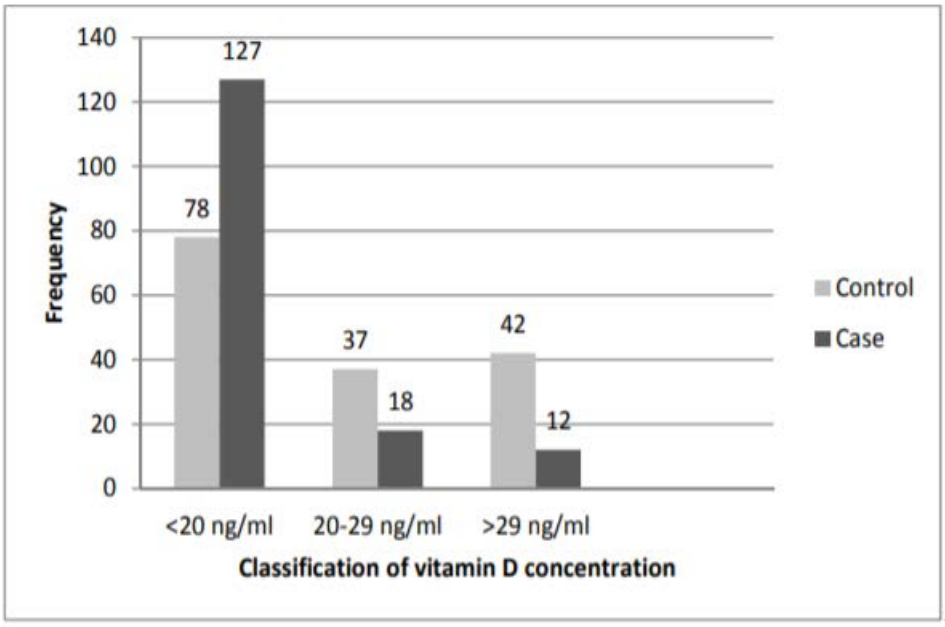

Figure 2. Comparing frequency of case and control groups at different levels of vitamin D concentration

ORs (Odds ratios) of vitamin D deficiency with present or absence of PCOS in infertile women are presented in Table 3.

Table 3. Odds ratio of infertility with changing serum vitamin D concentrations

	P value	OR	95% C.I. for EXP(B)	
			Lower	Upper
Vitamin D concentration [1]	0.001	0.96	0.934	0.975
Vitamin D concentration [2]	0.001	0.95	0.937	0.973

[1] *Not adjusted for age*
[2] *Adjusted for age*

As age significantly differed between the groups and to exclude its confounding effects, the multiple logistic regression models were implemented. The results showed that per increasing vitamin D levels by 1 unit the odds of infertility due to PCOS decreased by 5.5% (OR= 0.95, CI95%=0.93-0.97, P<0.0001).

DISCUSSION

This retrospective study was conducted to compare and assess the prevalence of vitamin D deficiency in two groups of infertile women with and without PCOS, in Ahvaz, in south of IRAN. The seasonal values of vitamin D levels were measured, as well. We observed the majority of infertile women with vitamin D deficiency. The mean of vitamin D levels in PCOS women was significantly lower than non-PCOS women. In addition the highest mean of vitamin D concentrations was during autumn trimester of year in both groups whereas the lowest mean of vitamin D levels was observed during winter trimester of year in both groups (figure 2). Along with considering sunshine as the major source of vitamin D synthesis in the body (10), the adverse weather conditions during spring, summer and winter trimesters of the recent year at Ahvaz is the main cause of inadequate exposure to sunlight. Therefore, the higher mean serum vitamin D levels during the autumn trimester of year may be attributable to improving air temperature and consequently more exposure to sunlight. The high prevalent of vitamin D deficiency (about 69%) have been reported by several studies in Germany (10) and in North America (11, 12) as well. While the proportion of vitamin D deficiency in PCOS infertile women (80.8%) in this study is higher than the values reported by noted studies (10-12) whereas the proportion of vitamin D deficiency in infertile non-PCOS women (50.3%) is lower than the proportion (about 69%) in the previous studies (10-12).In present study, insufficient vitamin D status was observed in 15% and 22.5% of patients in PCOS infertile women and non-PCOS infertile women, respectively. Dressler et al. (10) conducted a study (2015) to determine the prevalence of vitamin D deficiency among infertile women. They have shown that vitamin D deficiency is highly prevalent among infertile women. In addition they have demonstrated the seasonal variations of vitamin D levels in deficient vitamin D group. Vitamin D deficiency is a global epidemic problem, and the role of vitamin D deficiency is women's reproduction is increasingly recognized (8). Even, vitamin D deficiency frequently noted in patients attending infertility clinics (10). Several rodent researches are demonstrated the importance of vitamin 25(OH)D in reproductive biology; however the role of vitamin D in human reproductive health relatively recent (10). There are a few studies and with small sample size evaluating the vitamin D deficiency in infertile women. Clinical trial studies assessing interventions with vitamin D or vitamin D3 analogous have shown improvement in follicle maturation, menstrual dysfunction and/or metabolic profile (1). Recently a study has reported that vitamin D deficiency is not associated with endocrine disorders such as endometriosis or PCOS, while their relationship with infertility is well-known (10, 25-27). We found opposite results which showed PCOS infertile women had lower vitamin D levels (13±11.5 ng/ml) in compare to non-PCOS women (25±20.7 ng/ml) (P<0.0001).

We also found that by increasing vitamin D levels the odds of PCOS decreased by 5.5% (OR=0.95, CI95%:0.93-0.97, P<0.0001). Recently, Dressler et al. have reported lower odds ratio than our study (OR=0.81, CI95%:0.39-1.67, P=0.57) (10). In contrast, by increasing in Vitamin D levels per 1 unit, the possibility of PCOS decreases by 96% was reported (13). It also demonstrated of 67 infertile patients of the study, 38% were with PCOS and vitamin D deficiency (<15 ng/ml), while 39% patients are non-PCOS vitamin D deficient(13). Furthermore, they have observed that only 7% of patients are with sufficient vitamin D status. Previously a high variable of vitamin D levels in PCOS infertile women was reported and 44% of patients were reported with vitamin D deficiency (13, 28-30). We similarly found a high variable range of vitamin D concentrations in case and control groups (0.5-89 ng/ml

and 2.1- 110 ng/ml, respectively).

Firouzabadi et al. (2012) in a clinical trial on vitamin D and calcium supplement in infertile PCOS patients have shown that 83% of patient experienced vitamin D deficiency and 35% are with severe vitamin D deficiency (1). Sadhir et al. (14) reported that 62.2% of the studied patients (with mean age of 15.2% yr) were with vitamin D deficiency. They have observed that mean serum vitamin D levels does not significantly differ between PCOS and health subjects, but they were not infertile. Similarly, Kim JJ et al. (15) did not detect difference between PCOS and health women regarding mean serum vitamin D and the prevalence of vitamin D deficiency.

The mean serum vitamin D levels in this study did not differ between trimesters of year in case group. Considering Ahvaz at a latitude of 31˚,20' N, it is expected that the population of this region have sufficient serum vitamin D status, but dust phenomena and warm weather which are the main characteristics of Ahvaz prevent individuals from exposure to sunlight. Hence, it may lead to low serum vitamin D concentrations in the studied populations. Recent studies (10, 16) have reported low levels of vitamin D even in trimesters of year with extreme sunlight. These may suggest that increasing vitamin D levels by exposing to sunlight may not be logic alternative for reproductive age women.

Our findings showing high prevalence vitamin D deficiency among infertile PCOS are in in consistence with global researches. Furthermore, we observed consistency between our findings and previous studies regarding the seasonal variations in vitamin D concentrations. In addition, vitamin D deficiency in infertile PCOS women is more prevalent than infertile non-PCOS patients. Therefore, we suggest measuring serum vitamin D in infertile PCOS and non-PCOS patients attending infertility clinics.

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