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PREVALENCE OF ABNORMAL VITAMIN D LEVELS IN PCOS AS COMPARED TO NON-PCOS WOMEN AND ITS CORRELATION WITH BMI: A CROSS-SECTIONAL STUDY

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ABSTRACT

Introduction: A recently identified and potentially important addition in PCOS is low level of vitamin D. A number of studies have demonstrated association between vitamin D level and various PCOS symptoms including insulin resistance, infertility and hirsutism. (18-22) The main purpose of this study is to determine prevalence of abnormal vitamin D levels in PCOS women attending a hospital, compare these levels with non-PCOS group and to find out any relationship between BMI and insulin resistance in vitamin D deficiency.

Materials and Methods: This observational study was carried out in the Department of Obstetrics and Gynaecology, B.R.Singh Hospital and Centre for Medical Education and Research, Eastern Railway, Howrah, West Bengal over a period of 15 months, among 90 consented women of age group 15-45 years who reported to the Gynaecology OPD. 60 were selected as cases and 30 as controls. Detailed history was recorded, general examination done, vitals recorded, anthropometric measurements were taken and hormonal and biochemical assays were carried out, apart from the ultrasound investigation. Data was collected, compiled and analysed using Epi Info (TM) 3.5.3. χ^2 test, Z-test and T-test were used wherever necessary. p-value< 0.05 was considered statistically significant.

Result: Mean age of the PCOS patients was 27.13±5.59 years and majority (56.7%) were between 21-30 years. Mean age of control group was 28.36±5.69 years. Menstrual irregularities and hyperandrogenemia were more common among PCOS women. Menstrual cycle per year among women with PCOS had a mean of 5.63±0.78. Hirsutism and acne were also found more in PCOS women. 61.7% PCOS women had acne and the mean serum testosterone levels were 6.65±36.31ng/ml. BMI was seen to have a significant association with PCOS. Mean BMI of PCOS women was 26.89±4.19. Mean BMI of the control group was 23.07±2.57. All the patients with Vitamin-D deficiency had PCOS. The prevalence of Vitamin-D deficiency among the patients with PCOS was 11.7%. Mean level of Vitamin D in PCOS patients was significantly lower than that of patients without PCOS. ($p<0.001$). Among the PCOS women 11.7% were deficient in Vitamin D, 83.3% had insufficient level and 5% had optimal levels. The mean levels of vitamin D was 12.57±4.06 ng/ml with a median and range of 12.01ng/ml and 5.40-24.30ng/ml respectively. Among the control group 80% had insufficient levels and 20% had optimal levels of vitamin D. They had a mean of 15.25±4.78 ng/ml and a range of 8.25- 25.40ng/ml. The risk of deficiency or insufficiency of Vitamin D was 4.75 times more among patients with PCOS as compared to patients without PCOS and the risk was significant [OR-4.75 (1.09, 20.57);p=0.025].

Conclusion: It is important to screen all PCOS women for vitamin D levels for early intervention. As obese PCOS patients are at a greater risk of Vitamin D deficiency and its later morbidity, they should be followed up more frequently and be advised about weight reduction by lifestyle changes and dietary modification with the inclusion of high protein calcium and vitamin D rich diet and exclusion of fried and oily food items. Vitamin D supplements may be considered in treatment of PCOS women having altered vitamin D levels.

Key words: PCOS, Vitamin D, BMI, WHR

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INTRODUCTION: Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder affecting women in reproductive age group. It is characterized by the presence of chronic history of oligomenorrhoea or anovulation, hyperandrogenism (clinically- hirsutism or acne: biochemical- elevated androgen) and presence of polycystic changes in ovary, along with features of obesity and insulin resistance. [1, 2] The prevalence of PCOS varies from 5-10% in the reproductive age group [3, 4, 5] and may present up to 18% of this population.[6] Symptoms include features of Hyperandrogenism like Hirsutism, Acne, Alopecia, Seborrhea; Manifestations of Ovarian Dysfunction like Oligomenorrhoea, Amenorrhoea and Polycystic appearance in ultrasound. It is also associated with cardiovascular and metabolic disorders like hypertention, dyslipidemia, coronary artery disease, subclinical atherosclerosis, impaired glucose intolerance, type II diabetes mellitus and obesity. [7, 8, 9] PCOS is also associated with mood disorders such as depression and anxiety. [10]

A recently identified and potentially important addition in PCOS is low level of vitamin D. A number of studies have demonstrated association between vitamin D level and various PCOS symptoms including insulin resistance, infertility and hirsutism. [11-15] Vitamin D is thought to influence the development of PCOS through gene transcription. A level of 20ng/ml to 50ng/ml is considered adequate for healthy people. Several studies have reported low level of vitamin D in women with PCOS, with average 25- hydroxyvitamin (25-OHD) levels between 11 and 31ng/ml [11-13, 16, 17-22] with majority having values less than 20ng/ml (67 to 85%). [12-14, 16, 18, 19] Most of PCOS woman are either overweight or obese and have central obesity. Obesity is associated with insulin resistance, hyperandrogenism and also with low vitamin D levels. [23]

The main purpose of this study is to determine prevalence of abnormal vitamin D levels in PCOS women attending a hospital, compare these levels with non-PCOS group and to find out any relationship between BMI and insulin resistance in vitamin D deficiency. It is noteworthy that there are very few studies done in Indian context showing the correlation of vitamin D level in PCOS women and its association with body weight. This study, thus, aims to fill this lacunae so that we can improve the quality of life of Indian population which are already more prone to nutritional and metabolite abnormality.

MATERIALS AND METHOD: This observational study was carried out in the Department of Obstetrics and Gynaecology, B.R.Singh Hospital and Centre for Medical Education and Research, Eastern Railway, Howrah, West Bengal, after approval by Institutional Ethics Committee over a period of 15 months. B.R. Singh Hospital mainly caters medical services to railway employee and their relatives residing in the eastern zone (West Bengal) and its adjoining regions, hence this was selected as our area of study. Consented women of age group 15-45 years who reported to the Gynaecology OPD were included in the study.

The sample size was calculated as follows:

Mean of Group 1- M1
Mean of Group 2- M2
Common Standard Deviation (SD) = σ
Difference per SD (DSD) = (M1-M2) /σ
(Absolute difference of M1 and M2 is used for calculation.)

As per the study by Kumar et al [24], mean level of Vitamin-D of patients with PCOS (n=80) and without PCOS (n=80) was 31.0 ± 10.6 ng/ml and 23.12 ± 11.2 ng/ml respectively. The pooled S.D. was σ = 10.90 and M1-M2= 7.88. Therefore, DSD = 7.88 / 10.90 = 0.72. From the sample size table, to detect an effect size of 0.72 there was a need of 30 study subjects per group with 80% power at 5% level of significance. Thus, there was a need of 30 study subjects per group. The number of patients in each group was in the ratio 2:1. Thus, the patients with PCOS were 60 and without PCOS were 30. So the required sample size for the study was 90. Patients of the two groups were selected with the help of computer generated random numbers by the process of randomization.

Presence of any two of three Rotterdam's criteria among the women was diagnosed as PCOS. Women in the age group of 15-45 years with 8 or more spontaneous cycles in a year, no clinical or biochemical evidences of hyperandrogenemia and normal ultrasound findings were taken as controls. All patients on oral contraceptive pills, oral hypoglyceamic agents or insulin, smokers, patients with congenital adrenal hyperplasia, cushing's disease, thyroid disorder, hyperprolactinemia were excluded from the study.

A detailed history was recorded, general examination was carried out, vitals recorded, anthropometric measurements were taken and hormonal and biochemical assays were carried out, apart from the ultrasound investigation.

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STATISTICAL ANALYSIS: Statistical Analysis was performed with help of Epi Info (TM) 3.5.3. EPI INFO is a trademark of the Centre for Disease Control and Prevention (CDC). Using this software, basic cross-tabulation, inferences and associations were performed. χ^2 test was used to test the association of different study variables with the study groups. Corrected chi-square (χ^2) test was used for any cell frequency found to be less than zero. Z-test (Standard Normal Deviate) was used to test the significant difference between two proportions. T-test was used to compare the means. Odds ratio with 95% confidence interval was calculated to assess the risk. p-value< 0.05 was considered statistically significant.

RESULTS:

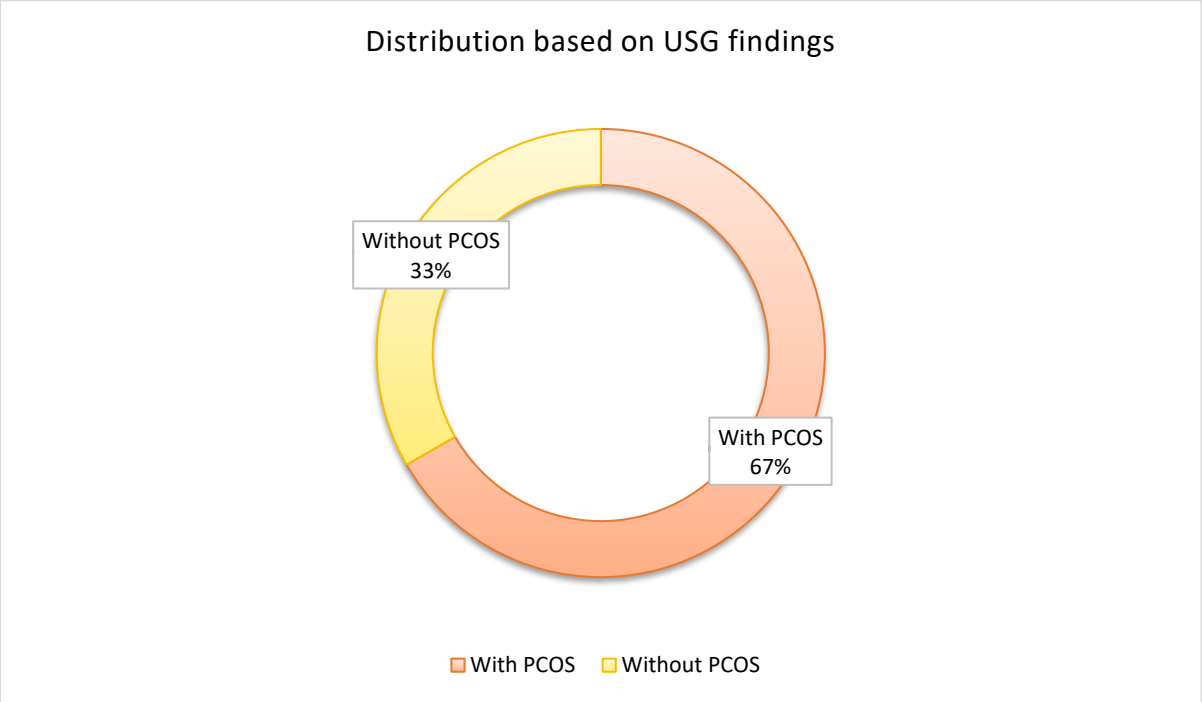

Figure 1: Distribution of patients based on USG findings

Table 1: Distribution of patients with and without PCOS on the basis of various parameters and findings

Parameters		With PCOS (n=60)		Without PCOS (n=30)		p-values
		No.	%	No.	%	
Age group	16-20 years	7	11.6%	2	6.6%	*0.72*
	21-30 years	34	56.7%	17	56.7%	
	31-40 years	19	31.7%	11	36.7%	
	Mean±SD (years)	*27.13±5.59*		*28.36±5.69*		*0.33*
	Median	*26*		*27.5*		-
	Range	*18-39*		*19-40*		-
Religion	Hindu	57	95%	27	90%	*0.37*
	Muslim	3	5%	3	10%	
Occupation	Housewife	25	41.6%	10	33.3%	*0.29*
	Professional	3	5%	3	10%	
	Service	10	16.7%	6	20%	
	Student	16	26.7%	11	36.7%	
	Unemployed	6	10%	0	0.00%	

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Marital Status	Married	37	61.7%	17	56.7%	*0.64*
	Unmarried	23	38.3%	13	43.3%	
Past Medical/ Surgical history	Appendectomy	4	6.6%	1	3.3%	*0.82*
	D/E	1	1.7%	0	0.00%	
	Lap cholecystectomy	2	3.3%	1	3.3%	
	LUCS	1	1.7%	0	0.00%	
	NS	52	86.7%	28	93.4%	
Obstetric History	P0+0	8	13.3%	2	6.7%	*0.07*
	P0+1	2	3.3%	0	0.00%	
	P1+0	6	10.0%	6	20.0%	
	P1+1	0	0.00%	1	3.3%	
	P2+0	7	11.7%	3	10%	
	P2+1	0	0.00%	1	3.3%	
	P3+0	0	0.00%	2	6.75	
	P4+0	0	0.00%	1	3.3%	
	NIL	37	61.7%	14	46.7%	
History of Allergy	Dust	1	1.7%	1	3.3%	*0.68*
	Sulpha drugs	1	1.7%	0	0.00%	
	NIL	58	96.6%	29	96.7%	
Age of menarche	9-10 years	14	23.3%	5	16.7%	*0.45*
	11-12 years	35	58.3%	15	50.0%	
	13-14 years	10	16.7%	9	30.0%	
	≥15 years	1	1.7%	1	3.3%	
	Mean±SD (years)	*11.38±1.23*		*11.83±1.39*		*0.12*
	Median	*11*		*12*		
	Range	*9-16*		*9-15*		
Menstrual Cycle	Regular	6	10%	30	100%	*<0.00001**
	Irregular	54	90%	0	0.00%	
Duration of Menstrual Cycle	2-4	44	73.3%	11	36.7%	*0.0007**
	5-7	16	26.7%	19	63.3%	
	Mean±SD (days)	*4.03±1.08*		*4.93±1.25*		*<0.001*
	Median	*4*		*5*		
	Range	*2-7*		*3-7*		
Number of menstrual cycles per year	3-5	22	36.7%	0	0.00%	*<0.0001**
	6-8	38	63.3%	14	46.7%	
	9-10	0	0.00%	16	53.3%	
	Mean±SD	*5.63±0.78*		*8.50±0.77*		*<0.001**
	Median	*6*		*9*		
	Range	*3-7*		*7-10*		
Acne	Yes	37	61.7%	3	10%	*<0.00001**
	No	23	38.3%	27	90%	
Hirsutism	Yes	11	18.35	0	0.00%	*0.008**
	No	49	81.7%	30	100%	
BMI	Underweight	1	1.7%	1	3.3%	*<0.001**
	Normal	4	6.7%	19	63.3%	
	Overweight	23	38.3%	3	10%	
	Obese	32	53.3%	7	23.3%	

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	Mean±SD	*26.89±4.19*		*23.07±2.57*		
WHR	>0.81	53	88.3%	10	33.3%	*<0.001**
	≤0.81	7	11.7%	20	66.7%	
Vitamin D	Deficient	7	11.7%	0	0.00%	*0.018**
	Insufficient	50	83.3%	24	80%	
	Optimal	3	5%	6	20%	
	Mean±SD	12.57±*4.06*		15.25±*4.78*		*<0.001*
	Median	12.01		14.99		
	Range	5.40-24.30		8.21-25.40		
FG Score	***Mean±SD***	11.80±5.09		3.90±1.19		*<0.001**
FBS (gm/dl)	***Mean±SD***	89.03±14.70		88.97±14.17		*0.98*
PPBS (gm/dl)	***Mean±SD***	110.50±22.36		107.93±16.05		*0.57*
Fasting Insulin (IU/ml)	***Mean±SD***	18.15±8.82		9.03±4.56		*<0.001**
HOMA	***Mean±SD***	4.00±2.04		2.00±1.10		*<0.001**
LH-FSH Ratio	***Mean±SD***	1.00±0.88		1.70±0.63		*<0.001**
Testosterone (ng/ml)	***Mean±SD***	6.65±36.31		0.74±0.63		*0.37*
DHEAS (mcg/dl)	***Mean±SD***	184.45±105.07		153.98±56.79		*0.14*
TSH(mU/l)	***Mean±SD***	2.63±5.2		2.66±1.16		*0.39*
Prolactin (ng/ml)	***Mean±SD***	15.48±7.01		13.58±5.59		*0.21*
17 OHP	***Mean±SD***	0.66±0.06		NA		*NA*

Table 2: Association of BMI and WHR with Vitamin D levels

Parameters		**Level of Vitamin D**						**p-values**
		Deficient		**Insufficient**		**Optimal**		
		No.	**%**	**No.**	**%**	**No.**	**%**	
BMI	Underweight	0	0.00%	1	1.4%	1	11.1%	*0.02**
	Normal	1	14.3%	16	21.6%	6	66.7%	
	Overweight	2	28.6%	22	29.7%	2	22.2%	
	Obese	4	57.1%	35	47.3%	0	0.00%	
WHR	>0.81	6	85.7%	55	74.3%	*2*	*22.2%*	*0.02**
	≤0.81	1	14.3%	19	25.7%	*7*	*77.8%*	

DISCUSSION:

Out of 60 PCOS subjects, 11.7% were <20 years of age, 56.7% were between 21-30 and 31.7% were >30 years of age. The mean age of the patients was 27.13±5.59 years with a range of 18-39 years. Mean age of control group was 28.36±5.69 years with a range of 19-40 years. This shows that even though PCOS is a disorder of reproductive age group, majority of the patients were <30 years of age. These findings are similar to **Knochenhauer ES et al** [(4)] where mean age was 29.4±7.1 in whites and 31.1±7.8 years in black women respectively. Similar study performed by **Azziz R et al** [(25)] also showed mean age of 29.1±7.2 years. In this study it was found that religion had no significant association with the disease. 61.7% were married and 38.3% were unmarried in PCOS group. In control group 56.7% were married and 43.3% were unmarried. There was no significant association between marital statuses of the two groups. In a study conducted by **Ramanand SJ et al** [(26)], of the 120 patients studied, 47 were married and 73 were unmarried. Marital status was not seen to play any role in the disease outcome. Menstrual irregularities and hyperandrogenemia were more common among PCOS women in the present study. Menstrual cycle per year among women with PCOS had a mean of 5.63±0.78 cycles per year. Hirsutism and acne were also found more in PCOS women. 61.7% PCOS women had acne and the mean serum testosterone levels were 6.65±36.31ng/ml. These findings were similar to the studies conducted by **Gambineri A et al** [(27)] and **A Majumdar et al** [(28)]. In the present study BMI was seen to have a significant association with PCOS. It was noted that 1.7% was underweight, 6.7% was normal, 38.3% was overweight and 53.3% was obese among the PCOS women. Mean BMI of PCOS women was 26.89±4.19. In the control group 3.3%, 63.3%, 10%, 23.3% belonged to the underweight, normal, overweight and obese category respectively. The mean BMI of the control group was 23.07±2.57. Studies carried out by **Fruzettietal** [(29)], **Dimanti Kandarakisetal** [(30)] suggested that obesity is more prevalent in women suffering from PCOS, similar to the present study. The main aim of the present study was to show abnormal vitamin D levels in PCOS women compared to non PCOS group. It was found that all the patients with Vitamin-D deficiency had PCOS. The prevalence of Vitamin-D deficiency among the patients with PCOS

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was 11.7%. Mean level of Vitamin D in PCOS patients was significantly lower than that of patients without PCOS. ($p<0.001$). Among the PCOS women 11.7% were deficient in Vitamin D, 83.3% had insufficient level and 5% had optimal levels. The mean levels of vitamin D was 12.57±4.06 ng/ml with a median and range of 12.01ng/ml and 5.40-24.30ng/ml respectively. Among the control group 80% had insufficient levels and 20% had optimal levels of vitamin D. They had a mean of 15.25±4.78 ng/ml and a range of 8.25- 25.40ng/ml. The risk of deficiency or insufficiency of Vitamin D was 4.75 times more among patients with PCOS as compared to patients without PCOS and the risk was significant [OR-4.75 (1.09, 20.57);p=0.025]. A study conducted by **Li et al** [16] reported a lower level of vitamin D in women with PCOS compared with women without PCOS (11ng/mlin PCOS group vs 17ng/ml in control group). Another study conducted by **Wehretal** [23] also reported lower levels in women with PCOS (n=85) compared to control group (n=145) 25.7ng/ml vs 32ng/ml, respectively, similar to present study. However, a study conducted by **Mahmoudietal** [17] comparing women with PCOS (n=85) to control group (n=115) of similar age (30years) and BMI (27kg/m2), found that women with PCOS had significantly higher vitamin D levels (29.3ng/ml in PCOS vs 19.4 in control group) Thus there is inconsistency in literature about whether vitamin D levels are similar between women with and without PCOS. In the present study it was also found that vitamin D levels were lower in PCOS patients more so in the obese group. Among the obese PCOS patient 10.63% had deficient levels, 89.7% had insufficient levels and none had optimal levels. Whereas among the overweight PCOS patients 7.7% had deficient levels, 84.6% had insufficient levels and 7.7% had optimal levels. However it should be kept in mind that vitamin D deficiency is also common in general population. [31,32] Out of 30 control taken 80% had vitamin deficiency or insufficiency and only 20% showing optimal vitamin D levels.

CONCLUSION: PCOS women with higher BMI are more prone to have to have glucose intolerance and insulin resistance. They also have higher incidence of higher testosterone levels, hirsutism, acne, and lower vitamin D levels. It is important to screen all PCOS women for vitamin D levels for early intervention. As obese PCOS patients are at a greater risk of Vitamin D deficiency and its later morbidity, they should be followed up more frequently and be advised about weight reduction by lifestyle changes and dietary modification with the inclusion of high protein calcium and vitamin D rich diet and exclusion of fried and oily food items. Vitamin D supplements may be considered in treatment of PCOS women having altered vitamin D levels.

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