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Hormonal Profile of Polycystic Ovary Syndrome (PCOS) In Indian Women

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ABSTRACT

Hormonal profile of PCOS was studied in 102 Indian women. Serum levels of Luteinizing hormone (LH), Follicle stimulating hormone (FSH), LH:FSH ratio, Prolactin (PRL), Thyroid stimulating hormone (TSH), Dehydroepiandrosterone (DHEA), Testosterone, fasting blood glucose (FBG), fasting insulin levels and Homeostasis Model Assessment (HOMA) value were estimated. The mean LH and FSH levels are 12.54 ± 5.87 and 5.70 ± 1.80 (IU/L) respectively. The mean LH : FSH ratio is reversed and is more than two (2.23±0.94). Mean PRL, TSH, and testosterone levels show normal ranges. Mean fasting insulin (16.27±13.27 mU/ml) and HOMA (3.509±2.621) are high with 79.31% prevalence of insulin resistance. In all the patients, both LH and FSH are positively correlated with testosterone. In normal weight patients, PRL and LH: FSH are positively correlated. In overweight/obese serum LH and DHEA are positively correlated. A positive correlation is observed between testosterone and PRL in overweight/obese. On sub-grouping data of gonadotropin levels with respect to different days of menstrual cycle, LH levels and LH:FSH ratio but not FSH levels show significant intergroup variation. The authors conclude that, low levels of FSH is persistent irrespective of day and phases of menstrual cycle, the reversal of LH : FSH is mainly because of lower FSH and the physiological cyclical pattern of gonadotropin is altered in PCOS with partial preservation of the cyclical variation of LH but not of FSH. Insulin resistance is independent of BMI and is common in Indian PCOS women.

Keywords: PCOS, Hormonal profile, Glucose Homeostasis, Correlation.

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting 5-10% of reproductive age women. The prevalence among the general female population is about 10% [1]. The gonadal hormonal homeostasis in PCOS women is altered. Disturbed gonadal cycle in PCOS manifests as persistent anovulation and irregular menses (oligomenorrheoa, amenorrhea) and infertility. The other clinical features of PCOS are signs and symptoms of hyperandrogenism (HA) like hirsuitism, acne and baldness. Insulin resistance and acanthosis nigricans are also common.

Depending on the pathogenesis and the interactions among different hormones, the clinical presentation and biochemical profile varies in an individual PCOS woman. All features of this syndrome may not be present in an individual patient. Due to its non uniform nature, defining PCOS has always been a challenging task. The diagnosis of polycystic ovaries earlier was based on visualization of the ovaries on laparatomy. The diagnosis was confirmed on biopsy and histological studies. Further research revealed the association of endocrine abnormalities with histological presentation typical of this syndrome and biochemical criteria were set for the diagnosis of PCOS. The consensus on a single biochemical or clinical definition for PCOS was hindered by the heterogeneous presentation of the syndrome. Ultrasonography (USG) to scan the morphology of the ovaries was a new addition in the diagnostic armament and has been accepted as a routine diagnostic method because of its very noninvasive nature. However, identification of polycystic ovaries by ultrasound alone does not confirm the diagnosis of PCOS. Nevertheless there is markable concordance between results of studies wherein diagnoses have been based on USG criteria and the results of those in which the PCOS has been defined on the basis of clinical and biochemical criteria[2]. Irrespective of the underlying endocrinological abnormality, the morphological findings in PCOS on USG are similar. This limits the role of USG in elucidating the etiological factor/s and therapeutic targets.

In spite of large number of studies in the field of research on PCOS, long term effects and treatment of PCOS remains a challenge. The treatment is targeted towards regularization of menses and infertility. As PCOS women are at high risk of developing insulin resistance, type II diabetes, dyslipidemia, premature arteriosclerosis and endometrial carcinoma, in addition to symptomatic relief correction of the underlying endocrinological pathology and biochemical abnormalities at the earliest is necessary. An ethnic variation in PCOS had also been reported [3,4].

Hormonal profiling forms an important tool to elucidate basic pathogenesis of PCOS. Moreover it may help in decision making as regards to treatment modalities required for better outcome and can also be used for differential diagnosis. In addition to clinical prognosis, changes in hormonal profile may assist the assessment of efficacy of therapy.

In the light of this background the current study was conducted to know hormonal profile and status of glucose homeostasis in Indian PCOS women.

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MATERIALS AND METHODS

Study design and study subjects

This prospective cross sectional study was carried out over the period of one and half year. Newly diagnosed 102 postpubertal PCOS patients consulting endocrinology hospital for the complaints of irregular menses and or infertility were enrolled as per the inclusion and exclusion criteria after written informed consent. The diagnosis of PCOS was fulfilled when two of the following three clinical features were present: clinical or biochemical evidence of hyperandrogenism, chronic anovulation, and imaging of polycystic ovaries [1]. Patients having any major systemic illness, congenital adrenal hyperplasia, hyper prolactinemia, acromegaly, thyroid dysfunction and functional hypothalamic amenorrhea based on clinical findings and laboratory investigations were excluded. Pregnancy was ruled out whenever necessary. As per the Standard Consensus Statement of body mass index (BMI) for Indian population, patients were grouped as normal weight(18.0-22.9),overweight (23.0-24.9) and obese(≥ 25) [5]. For analysis, overweight and obese patients were included in a single group. The study was approved by the Institutional Ethics Committee. All the guidelines of Helsinki were followed. The patients were investigated for the laboratory parameters viz. serum LH, FSH, PRL, TSH, DHEA, testosterone, FBG and fasting insulin. Fasting blood sample was collected between 9 am to 12 noon. For the analysis of LH,FSH and LH:FSH ratio at different days of menstrual cycle , patients were divided into five groups based on days of menses viz. – group I- day 1-5, group II- day 6-12, group III- day 13-16, group IV- day 17-36, group V- day36+ .

Assay methods and normal laboratory values

In vitro quantitative determination of hormones was carried by electrochemiluminescence immunoassay method (Cobas e 411). Blood glucose was measured on autoanalyser (Microlab 300) using oxidase method. The normal values for different parameters are as Table 1.

Table 1: Normal values for different hormones and glycemic status

Parameter	Normal values
LH	During follicular and luteal phase: 5(IU/L), at ovulation: 60(IU/L)
FSH	During follicular and luteal phase: 10(IU/L), at ovulation: 15:20(IU/L)
LH:FSH (At different days of menses)	Day 5 : 0.7, day 6 to12 : 1.1
PRL	<15 (ng/dl). In absence of galactorrhea upto 35-50 (ng/dl) taken as normal
TSH	0.4-4.2(µg/dl)
DHEA (As per age)	18 to 19 years: 145-395(µg/ml), 20 to 29 years: 65-380(µg/ml) 30 to 39 years:45-270(µg/ml)
Testosterone	0.5-1.1 (ng/ml)
FBG	70-120(mg%)
Fasting insulin	< 13(mU/ml)
HOMA	> 1.9 indicates insulin resistance

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Statistical tests

Data was analyzed using computer software (Graph pad prism version 5). Intergroup comparison is done by unpaired 't' test (nonparametric – Mann Whitney) and Anova test. Correlation between various parameters has been analyzed by Spearman test p value less than .05 is considered significant.

RESULTS

Mean age of the study population was 21.74±4.31 years (range : 14 to 33 years). Twenty four patients had normal weight and 84 patients were overweight / obese.

Mean serum levels of hormones

Table 3: **Serum concentrations of hormones and glycemic status in PCOS women**

Parameter	Number of patients	Mean±SD	Range	95% CI
LH (IU/L)	102	12.54±5.871	1.680-31.05	11.39-13.70
FSH (IU/L)	102	5.707±1.807	1.430-13.52	5.353-6.062
LH:FSH ratio	102	2.239±.9450	0.471-5.844	2.053-2.424
PRL (ng/dl)	97	12.91±6.167	2.070-36.80	11.67-14.15
TSH(µg/dl)	86	2.409±1.167	0.164-6.430	2.159-2.659
DHEA(µg/ml)	60	360.9±238.6	31.90-980.0	299.3-422.6
Testosterone (ng/ml)	41	0.4733±.3788	0.005-2.050	0.353-0.592
FBG (mg%)	29	89.73±12.50	86.90-111.0	84.98-94.49
Fasting Insulin (mU/ml)	29	16.27±13.27	3.130-65.05	11.22-21.31
HOMA	29	3.509±2.621	0.646-13.20	2.512-4.506

SD- standard deviation, CI- confidence interval

Table 3 shows details of mean serum hormone levels, mean FBG and HOMA in patients of PCOS. FSH is lower than the normal values. The LH:FSH ratio is more than two. Mean PRL, TSH, DHEA and testosterone levels are within normal ranges. Mean fasting insulin level is high and HOMA is more than 1.9.

Serum gonadotropin at different days of menstrual cycle

Table 5 shows mean levels of LH, FSH and LH:FSH ratio at different days of menstrual cycle. The mean LH level is minimum at day 1-5(group I) and maximum at day 13 -16(group III). It differed significantly at different days of menstrual cycle. The mean FSH level is minimum at day 1-5(group I) and maximum at day 13-16(group III). FSH levels do not show significant variation in different groups. The LH / FSH ratio differed significantly at different days of menses.

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Table 5: Serum LH, FSH concentration and LH:FSH ratio at different days of menstrual cycle in PCOS women

Group	Day of menses	Mean LH (IU/L)	Mean FSH (IU/L)	Mean LH:FSH ratio
I ((10)	1-5	6.57±3.18	5.11± 0.69	1.30±0.67
II ((18)	6-12	11.33±4.32	5.95±1.71	1.90±0.53
III ((7)	13-16	15.46±6.62	6.60±1.85	2.39±0.90
IV ((29)	17-36	14.13±55.78	5.87±2.10	2.51±0.90
V ((38)	36 +	12.94 ±6.18	6.57±3.18	2.38±1.02
Across groups, p value	-	0.003 **	0 .508	0 .0005 ***

,*- highly significant.

Comparison between normal weight and overweight/obese PCOS women shows that, the LH, LH:FSH ratio, PRL, DHEA, testosterone and FBG levels are higher in normal weight PCOS women and difference between LH:FSH ratio is highly significant. Overweight/obese women show higher values of FSH, fasting insulin and HOMA. The difference between fasting insulin levels is significant (Table 4). The difference between proportion of normal weight and overweight/obese PCOS women, showing normal and high normal PRL is significant (Table 10). Though the difference between insulin levels in overweight/obese and normal weight groups is significant, proportion of normal weight and overweight/obese PCOS women showing raised HOMA is comparable and insulin resistance in these patients is independent of obesity(Table 11).

Correlation among different parameters

Table 6: Correlation between serum LH and FSH levels at different days of menses in PCOS

Group	Days of menses	Correlation coefficient	p value
I ((10)	1-5	0.284	0.4250
II ((18)	6-12	0.764	0.0002***
III ((7)	13-17	0.357	0.4316
IV ((29)	17-36	0.576	0.0011**
V ((38)	36+	0.600	< 0.0001***
Across groups ((102)		0.583	< 0.0001***

*significant. ** ***highly significant

In PCOS women LH levels show highly significant positive correlation with FSH, LH:FSH ratio and a significant positive correlation with testosterone. FSH is positively correlated with testosterone (Table 7). Table 6 shows correlation between LH and FSH at different days of menses. LH and FSH are positively and significantly correlated in group II (day 6-12), group IV (day 17-36) and groupV (day 36+). The correlation is absent in group I (day 1-5) and group III (day 13-16). The positive correlation between LH and FSH across the groups is highly significant. In normal weight PCOS women LH is positively correlated with FSH and LH:FSH ratio. FSH shows negative correlation with LH:FSH ratio. PRL shows positive correlation with LH:FSH ratio(Table8). The positive correlation between LH and FSH in overweight/obese PCOS women

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is highly significant. In these patients, LH, FSH , LH:FSH ratio and PRL are positively correlated with testosterone. LH, LH:FSH ratio are also positively correlated with DHEA (Table 9).

Table 7: Correlation among different hormones, glycemic status in PCOS women

	LH IU/L	FSH IU/L	LH:FSH ratio	PRL (ng/dl)	TSH (ng/dl)	DHEA (µg/ml)	Testosterone (ng/ml)	Fasting Insulin (mU/ml)
FSH IU/L	0.583 ***(102)							
LH:FSH ratio	0.707 ***(102)	-0.059 (102)						
PRL (ng/dl)	0.041 (97)	-0.065 (97)	0.179 (97)					
TSH(ng/dl)	-0.004 (86)	0.050 (86)	-0.016 (86)	-0.220 (82)				
DHEA (µg/ml)	0.130 (60)	0.025 (60)	0.180 (60)	0.105 (59)	-0.018 (51)			
Testosterone (ng/ml)	0.475 **(40)	0.406 **(40)	0.298 (40)	0.336 * (39)	0.198 (30)	0.232 (34)		
Fasting Insulin (mU/ml)	-0.001 (29)	0.075 (29)	-0.165 (29)	0.007 (28)	0.198 (25)	-0.119 (19)	-0.589 (15)	
HOMA	-0.015 (29)	0.092 (29)	-0.195 (29)	0.145 (28)	0.150 (25)	-0.024 (19)	-0.025 (15)	0.961 ***(29)

The above Table shows values of correlation coefficient ('r').Figures in bracket indicates number of patients, *- significant correlation,
,* - highly significant correlation.

Table 8: Correlation among different hormones, glycemic status in normal weight PCOS women

	LH IU/L	FSH IU/L	LH:FSH ratio	PRL ng/dl	TSH µg/ml	DHEA (µg/ml)	Testosterone (ng/ml)	Fasting Insulin (mU/ml)
FSH IU/L	0.464 * (28)							
LH:FSH ratio	0.502 ** (28)	-0.466 * (28)						
PRL(ng/dl)	-0.056 (27)	-0.271 (27)	* 0.389 (27)					
TSH(µg/ml))	-0.106 (23)	-0.178 (23)	0.093 (23)	-0.328 (22)				
DHEA(µg/ml)	-0.257 (17)	-0. 053 (17)	-0.205 (17)	0.073 (16)	0.065 (13)			
Testosterone (ng/ml)	0.251 (9)	0.108 (9)	-0.418 (9)	-0.410 (9)	-0.142 (6)	-0.142 (8)		
Fasting Insulin (mU/ml)	0.600 (6)	-0.142 (6)	0.371 (6)	-0.200 (6)	0.300 (5)	0.200 (4)	0.500 (3)	
HOMA	0.600 (6)	0.028 (6)	0.857 (6)	-0.028 (6)	0.200 (5)	0.400 (4)	0.991 (3)	0.828 (6)

The above table shows values of correlation coefficient. Figures in the bracket indicates number of patients, * - significant correlation.

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Table 9: Correlation among different hormones, glycemic status in overweight/obese PCOS women

	LH IU/L	FSH IU/L	LH:FSH ratio	PRL ng/dl	TSH µg/ml	DHEA (µg/ml)	Testosterone (ng/ml)	Fasting Insulin (mU/ml)
FSH IU/L	0.648 *** (74)							
LH:FSH ratio	0.774 *** (74)	0.127 (74)						
PRL(ng/dl)	0.039 (70)	0.027 (70)	0.009 (70)					
TSH(ng/dl)	0.079 (63)	0.108 (63)	0.046 (63)	-0.169 (60)				
DHEA(µg/ml)	0.372 * (43)	0.102 (43)	0.387 * (43)	0.114 (43)	-0.068 (38)			
Testosterone (ng/ml)	0.535 ** (31)	0.452 * (31)	0.399 * (31)	0.399 * (30)	0.223 (24)	0.262 (27)		
Fasting Insulin (mU/ml)	-0.088 (23)	0.0400 (23)	-0.383 (23)	0.136 (22)	0.084 (20)	-0.0428 (15)	-0.109 (13)	
HOMA	-0.077 (23)	0.067 (23)	-0.388 (23)	0.237 (22)	0.090 (20)	-0.003 (15)	-0.170 (13)	0.962 *** (23)

The above Table shows values of correlation coefficient ('r').Figures in bracket indicates number of patients, * significant correlation, **,*** - highly significant correlation

Table 10: Prolactin status in normal weight and overweight/obese PCOS women

Serum PRL(ng/ml)	Normal weight	Overweight/obese
Normal (<15)	12	15
High normal (15-35)	14	55
Total	26	70

p value - 0.0224* (Sig)

Table 11: Status of insulin resistance in normal weight and overweight/obese PCOS women

HOMA	Normal weight PCOS(number)	Overweight/obese PCOS(number)
Normal	2	4
Raised	4	19
Total	6	23

Analysed using Fischer.s test
p value - 0.5750 (Not-significant)

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DISCUSSION

Gonadotropins

A normal reproductive hormonal cycle in women is characterized by fluctuating gonadal hormonal levels, well regulated by hypophyseal-pituitary-gonadal axis. This is replaced by a relatively steady state of gonadotropin associated with persistent anovulation.

Table 2: Modal class (class with highest frequency) values of different parameters in PCOS women

Parameter	Modal class value	Frequency of occurence	% occurence
LH (IU/L)	10-15	35	34.31
FSH (IU/L)	3-6	55	53.92
LH:FSH ratio	2.0-2.8	40	39.21
PRL (ng/dl)	6-12	47	48.45
TSH(µg/dl)	2-3	31	36.04
DHEA(µg/ml)	150-300	31	51.66
Testosterone (ng/ml)	0.4-0.8	21	51.21
FBG (mg%)	90-100	12	41.37
Fasting Insulin (mU/ml)	1-10	12	41.37
HOMA	2.0-3.5	12	41.37

The present study shows that, in Indian PCOS women high LH:FSH ratio is a common occurrence . Also the occurrence of low levels of FSH and higher LH: FSH ratio is very frequent. (Table 2). The mean FSH level is low as compared to normal values given for any day of menstruation and LH: FSH ratio is raised (Table 3). This is in accordance to Chang et al who had reported that the ratio of LH to FSH in PCO patients was 2.9 compared to a value of 1.1 in the normal group[6]. The gonadotropin releasing hormone (GnRH) pulse frequency designates the preferential production of LH via high frequency pulses versus FSH via low frequency pulses in normal adult women. The pulse frequency is regulated by progesterone in presence of estradiol such that increased progesterone production by corpous luteum slows LH pulse frequency to favor FSH production, which aids in follicular development for the next menstrual cycle. Women with PCOS have abnormally rapid LH pulses with reduced response to progesterone feedback, contributing to elevations in LH:FSH ratios [7]. Hayes FJ et al concluded that the data of their study on the assessment of neuroendocrine and androgen dynamics imply that, the enhanced pituitary sensitivity is responsible for the elevated LH amplitude in PCOS [8].

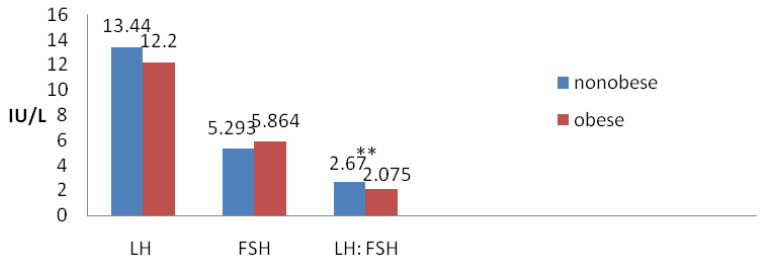

Figure 1: Comparison of mean serum LH, FSH levels and LH:FSH ratio in obese and nonobese PCOS patients.

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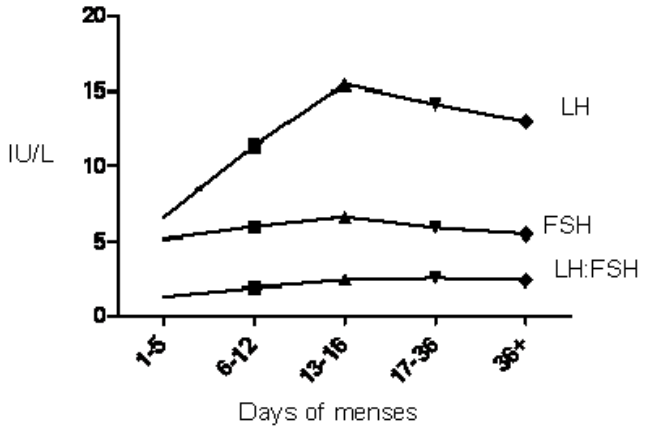

Figure 2: Mean LH, FSH and LH; FSH ratio at different days of menses

Considering physiological cyclical changes in gonadotropin levels we divided the data of gonadotropin concentrations in five different groups depending upon the days of menstrual cycles. (Table 5, Figure 2). The present data shows that, the mean LH level is higher during follicular and luteal phase as compared to physiological referral values. This is in accordance to previous studies. Ventiroli S et al observed high mean LH values in PCOS patients 27.9 ± 5.9 IU/1) at day 5-6 of menses [9]. In the present study it is not very high as compared to physiological values at day 13-16 indicating a lack of physiological ovulatory surge. It is also possible that due to irregular cycles the sample collection was not matched with the physiological surge. At day17-36 and 36+, the mean LH levels are high as against expected physiological drop. This is in accordance to the well accepted concept of persistent higher levels of LH in PCOS. The mean FSH levels in the present study at different days of menstrual cycle are lower than the physiological referral values. Holte J et al found lower FSH levels in women with PCOS than during the early follicular phase of normally ovulating women, suggesting a role in anovulation in PCOS [10]. The difference between minimum (group I) and maximum (group III) levels is very less. The normal physiological rise during mid cycle (group III) is not observed. The mean FSH levels do not differ significantly at different phases of menstrual cycle and are comparable in all the groups. We compared LH:FSH ratio at different days of menstrual cycle. 16 patients have LH:FSH ratio of more than three (GpII-1,GpIII-1,Gp IV- 6 and GpV-8.). High ratio is common in patients having prolonged amenorrhea. The significant variation in LH/ FSH ratio at different days of menstrual cycle is mainly due to different LH levels in presence of comparable FSH levels.

When normal weight and overweight/ obese patients were compared, normal weight patients had higher mean LH and lower mean FSH levels (Table 4).Though these differences are insignificant, the LH:FSH ratio is significantly high in normal weight patients (Figure 1). Morales et al have shown that LH pulse frequency was accelerated in both lean and obese PCOS, whereas the mean 24-h LH pulse amplitude was increased in lean but not in obese PCOS patients [11]. Mc Cartney et al in the study in pubertal girls have reported that obesity in prepubertal and early pubertal girls is associated with reduced LH secretion and reduced nocturnal changes of LH. In latter pubertal girls, obesity is linked with reduced LH amplitude,

but elevated LH frequency; the latter may reflect effects of hyperandrogenemia [12]. It has been suggested that the overall reduction in LH may be a direct effect of greater hyperandrogenism in obese women, but in our overweight/obese patients testosterone and DHEA levels are not greater as compared to normal weight. Therefore lower LH and LH :FSH ratio in overweight/obese may not be attributed to hyperandrogenism.

As PCOS is an endocrine disorder having multifactorial, interlinked hormonal derangement, we tried to explore complex association of different parameters with one another irrespective of BMI (Table 7). A very highly significant positive correlation between LH and FSH is indicative of preservation of sensitivity of gonadotropes to stimulatory or inhibitory factors in PCOS without any discrimination between LH and FSH secreting cells. Correlation between LH and FSH levels across the group prompted us to further analyze the data with respect to days of menses (Table 6). LH and FSH levels positively and significantly correlated with each other in groups II, IV and V. No significant correlation was observed in group I and III. The positive correlation between LH and FSH across the groups is highly significant.

As our normal weight and overweight/obese patients show different hormonal profile, the correlation among different parameters is further analyzed dividing the data into subgroups of normal weight (Table 8) and overweight/obese patients (Table 9). The positive correlation of LH with FSH and the LH: FSH ratio is highly significant in overweight/obese women. This may be because of the higher number of overweight/obese patients. The negative correlation between FSH and LH: FSH ratio is preserved only in normal weight women.

The negative feedback control of FSH is critical for development of the single mature oocyte that characterizes normal reproductive function in women. Decreased levels of FSH in PCOS in the present study indicate persistence of this negative feedback to such an extent that not a single follicle is permitted to mature enough for ovulation to occur. We cannot comment on the role of factors modifying FSH responsiveness as the present study involves measurement of serum FSH levels alone. Nonetheless further studies in this regards are warranted.

The above results of present study should be considered given the fact that, the cycles in PCOS are anovulatory and irregular. However we attempted to show the possible hormonal imbalance in the form of abnormal LH and FSH secretion underlying the complex endocrinological cascade of PCOS. Though a persistent constant rise in LH levels is expected in PCOS, we have observed that the mean LH levels differed significantly at different phases of menstrual cycle, suggesting that the physiological cyclical hormonal regulation is not totally lacking.

DHEA and Testosterone

Though the mean DHEA is in normal range, DHEA is raised in 33.33% in our (20 of 60) patients. Out of 17 normal weight patients 8 had raised DHEA. 12 of 43 overweight/obese had raised values. This rise in DHEA is independent of obesity. This discrepancy may be because of wide normal range of DHEA.

DHEA is positively and significantly correlated with LH and LH: FSH ratio in overweight/obese patients. No significant correlation was observed between DHEA and other parameters both in normal weight and overweight/obese patients (Table 11, Table 10).

Our PCOS patients show mean testosterone within normal range. In the present study testosterone is positively and significantly correlated with LH, FSH and LH:FSH in overweight/obese patients. The correlation between testosterone and LH is highly significant. This may be because testosterone opposes the inhibitory feedback action of estrogen on the release of gonadotropins. According to Hayes FJ et al in PCOS the secretion of androgen is dependent of LH and testosterone levels fall within normal levels with the use of GnRH antagonists [8]. In adolescent PCOS girls LH is positively correlated with testosterone. Solorzano et al had postulated that in girls hyperandrogenism alters the inhibition of the Gonadotropin releasing hormone (GnRH) pulse generator, leading to high frequency pulse that favor LH production [13].

We postulate that DHEA as compared to testosterone plays a major role in the alteration of this pulse generator in overweight/obese PCOS; based on the results that testosterone is positively correlated both with LH and FSH and DHEA is positively correlated with LH but not FSH. This hypothesis does not explain the reversal of LH: FSH ratio in normal weight. We did not measure sex hormone binding globulin (SHBG) and free testosterone. Robinson S in a comparative study on PCOS and normal ovulatory controls has reported that, the SHBG did not differ significantly between the two groups. The authors add that, the combination of SHBG and testosterone to derive a free testosterone value did not further aid the biochemical diagnosis of PCOS [14].

Prolactin

Our PCOS patients show mean PRL within normal range.Normal weight patients show comparatively higher PRL values than the overweight/obese patients. On subgrouping PRL values in to normal and high normal, it is observed that, greater proportion of normal weight women had high normal levels. This difference between overweight/obese and normal weight is significant (Table 10).

A positive correlation of PRL with LH: FSH ratio in normal weight PCOS is observed in our study (Table 8). This along with a higher PRL levels is suggestive of significant role of PRL in PCOS in normal weight. Stress in association with other factors may be a contributor in these patients. Ventiroli S et al in their study on pulsatile secretion of FSH, LH, PRL in PCOS subjects observed that 75% of PRL pulses showed a temporal relationship with LH pulses [9]. Rise in PRL is associated with stress. In normal weight PCOS, increased PRL may have a permissive role in the pathophysiology of the syndrome. PRL inhibits reproductive function by suppressing hypothalamic GnRH and pituitary gonadotropin secretion and by impairing gonadal steroidogenesis in both women and men. In the ovary, PRL blocks folliculogenesis and inhibits granulosa cell aromatase activity, leading to hypoestrogenism and anovulation. PRL also has a

luteolytic effect, generating a shortened, or inadequate, luteal phase of the menstrual cycle [15]. An increased progesterone production by corpus luteum is needed for appropriate LH:FSH which aids the follicular development for the next menstrual cycle. We hypothesize in normal weight PCOS the effect of stress induced increased PRL is such that its lueteolytic effect results in an inadequate production of progesterone and the subsequent effect on LH: FSH ratio, altering it in favor of LH and against FSH. This hypothesis does not hold good for overweight/obese as the correlation between PRL and the LH:FSH ratio is lacking. We observed that in overweight/obese PCOS testosterone and PRL are positively and significantly correlated (Table 9). The correlation can be explained as above, i.e. PRL blocks folliculogenesis and inhibits granulosa cell aromatase activity leading to hypoestrogenism and anovulation. The result of present study is suggestive of the contribution of PRL in PCOS and its variant nature in normal weight and overweight/obese PCOS women.

TSH

The mean TSH in the present study is within normal range; as the patients with thyroid dysfunction were excluded. TSH show no correlation with any parameters in both normal weight and overweight/obese.

Glucose homeostasis

Assessment of glucose homeostasis in PCOS patients of the present study reveals that, though the mean FBG level is within normal range, more number of our patients (41.37 %) showed value on the higher side of the range i.e. between 90 to 100 mg%. Raised HOMA indicating presence of insulin resistance is also a very common occurrence (Table 2). The mean fasting insulin is high and insulin resistance indicated by raised HOMA is present in 79.31% subjects of the present study (23 of 29 patients). The prevalence of insulin resistance is comparable to that reported by Kalra A et al [16]. The authors in their study, on association of obesity and insulin resistance with dyslipidemia in Indian PCOS women have reported 76.9% prevalence of insulin resistance. Insulin levels are significantly higher in overweight / obese patients as compared to normal weight.

Higher fasting insulin and HOMA in overweight/obese prompted us to compare occurrence of insulin resistance (based on HOMA) in normal weight and overweight/obese patients (Table 11). The proportion of patients showing insulin resistance in normal weight and overweight/obese is comparable. Also the difference between mean HOMA in overweight/obese and normal weight is statistically insignificant. This indicates that the insulin resistance in PCOS women is independent of obesity. Our result is in accordance to the study by Andrea Dunaif et al.[17] The authors have demonstrated that the decrease in insulin sensitivity in PCOS cannot be explained by obesity and women with PCOS have a distinct disorder of insulin action not secondary to obesity. Decreased insulin sensitivity has been demonstrated in lean and obese PCOS women, suggesting that the defect is intrinsic to PCOS. But the degree of resistance is high in obese women as the insulin levels are greater in obese. Chang et al have well-documented that women with PCOS, independent of obesity, are insulin resistant and

have compensatory hyperinsulinemia as a result of their disorder[6]. However higher values of insulin as stated above in overweight/obese patients indicate, that excessive body weight in PCOS exacerbates or hastens the complications of the disease.

Insulin and HOMA were not correlated with LH, FSH and LH:FSH ratio. Though insulin resistance and hyperandrogenism are characteristics of PCOS, no significant correlation was observed between insulin, HOMA and testosterone, DHEA. This finding is similar to the report by Dunaif A et al [18]. The authors in a study on ethnicity and PCOS, have reported that circulating androgen levels were not significantly related to insulin levels or to insulin sensitivity in women of any study group. Our result is contradictory to the findings reported by Chang et al in a study on hirsute and oligomenorrhic normal weight PCOS patients. The authors had observed a positive correlation of serum testosterone and androstenindione levels to insulin secretion suggesting that the insulin resistance in PCO may be, in part, a consequence of hyperandrogenism[6]. The contradiction may be because of selection of PCOS patients, as we have included PCOS women irrespective of presence of hirsutism.

CONCLUSION

In PCOS women, normal gonadotropin-ovarian axis is disturbed. This is reflected by the higher levels of LH, lower FSH levels and reversal of LH: FSH ratio. Indian PCOS women show similar trend in this regards. FSH levels in PCOS show lower than normal values and are comparable at different days of menstrual cycle without significant variations. Androgen dynamics involving both testosterone and DHEA and its relation with gonadotropin is significant in overweight/obese PCOS. Hormonal milieu in normal weight and overweight/obese women differs. Prolactin may be influencing reproductive cycle in PCOS, may be through different ways in normal weight and overweight/obese PCOS. Insulin resistance is common in Indian PCOS women and this is independent of obesity. Further chronobiological studies with sequential estimations of hormones are warranted in Indian PCOS women to understand this complex interplay of different hormones.

REFERENCES

[1] Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Fertil Steril 2004; 81: 19-25.
[2] Stephen Franks. NEJM 1995; 333: 853-61.
[3] Wiliamson K, Gunn AJ, Johnson N, Milsom S. Aust N Z Obstet Gynaecol 2001; 41: 202-6.
[4] Norman RJ, Mahabeer S, Masters S. Fertil Steril 1995; 63: 58-62.
[5] Misra A, Chowbey P, Makkar BM, Vikram NK, Wasir JS, Chadha D, et al. JAPI 2009; 57: 163-70.
[6] Chang RJ, Nakamura RM, Judd HL, Kaplan SA. J Clin Endocrinol Metab 1983; 57:356.
[7] Pastor CL, Griffin-Korf ML, Aloi JA, Evans WS and Marshall JC. J Clin Endocrinol Metab 1998; 83: 582-90.
[8] Hayes FJ, Taylor AE, Martin KA, Hall JE. J Clin Endocrinol Metab 1998; 83: 2343-49.

[9] Venturoli S, Porc E, Fabbri R, Magrini O, Gammi L, Paradisi R et al. Clin Endocrinol 1988; 28: 93-107.
[10] Holte J, Bergh T, Gennarelli G, Wide L. Clin Endocrinol (Oxf) 1994; 41: 73-81.
[11] Morales AJ, Laughlin GA, Bützow T, Maheshwari H, Baumann G and Yen SS. J Clin Endocrinol Metab 1996; 81: 2854.
[12] McCartney RC, Prendergast KA, Chhabra S, Eagleson CA, Yoo R, Chang RJ et al. J Clin Endocrinol Metab 2006; 91(5):1714–1722.
[13] Solorzano CM, McCartney CR, Blank SK, Knudsen KL, Marshall JC. BJOG 2010; 117: 143-49
[14] Robinson S. Hormone for diagnosis of PCOS.BJOG 1992;99.
[15] Hall JE. The Female Reproductive System, Infertility and Contraception. In, Harrison's Principles of Internal Medicine. New York,Mc GrawHill Publishers,18th Edition, 2:3028-39
[16] Kalra A, Nair S, Rai L. Indian J Med Sci 2006; 60: 447-53.
[17] Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Diabetes 1989; 38: 1165-74.
[18] Dunaif A, Sorbara L, Delson R, Green G. Diabetes 1993; 42:1426-68.