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Evaluation of the association of insulin resistance with polycystic ovary syndrome

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Abstract
Background: A simple test for glycemic status and its correlation with clinical features of insulin resistance will be more cost effective in diagnosing and treating with insulin sensitizers for the metabolic syndrome in Polycystic ovarian syndrome (PCOS). Current study aimed to to study the association of insulin resistance in women with PCOS.
Method: In this cross sectional study, 50 PCOS patients who attended our outpatient department according to Rotterdams criteria and we determined the insulin resistance among them.
Result: In our study 42% of the cases were between 25-29 years of age. 72% of them were married. 46 % had BMI of 18-24 and another 46% had BMI of 25-30. 36% of our study population had positive family history of PCOS and only 6% had family history of both PCOS and Diabetes. 17% of the patients had oligomenorrhoea. 18 patients (36%) had positive insulin resistance in this study out of which 9 patients also had impaired glycemic status. This was found to be statistically significant with p value of <0.001. Out of 12 cases of clinically evident hirsutism 9 patients (75%) had positive insulin resistance giving a significant p value of 0.001. Also 18 cases with acanthosis had insulin resistance with p value <0.001.
Conclusion: Therefore all cases of PCOS with impaired glycemic status had insulin resistance and so by evaluating the glycemic status and other clinical parameters like hirsutism, acanthosis, abdominal obesity and menstrual irregularities were able to arrive at the diagnosis of insulin resistance among study population.

Keywords: Polycystic ovarian syndrome, hyperinsulinemia, insulin resistance, diabetes mellitus

1. Introduction
Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder among women of fertile age [1]. The prevalence of PCOS varies between 2.5 and 7.5%. Clinical manifestations include menstrual dysfunction and hyper androgenic symptoms, and it can be associated with metabolic dysfunction in which hyperinsulinemia and peripheral insulin resistance are central features. A significant proportion of women with PCOS have insulin resistance greater than that of their weight-matched controls. Furthermore PCOS is thought to present an early manifestation of the metabolic syndrome (or syndrome X), which is a cluster of abnormalities where the combination of insulin resistance and compensatory hyper insulinemia predisposes individuals to develop a high plasma triglycerides (Tg) and a low high-density lipoprotein (HDL) cholesterol concentration, high blood pressure and coronary heart disease [2].
The etiology of PCOS is still obscure. It has been well documented that inappropriate gonadotrophin secretion, especially high luteinizing hormone (LH) secretion, is associated with the classic form of PCOS.
Several studies have indicated that polycystic ovaries usually produce excess androgen [3]. The mechanisms leading to increased androgen production in PCOS are not completely understood. Chronic LH stimulation in PCOS induces sustained hyper secretion of androgens by theca compartment, probably augmented by insulin and insulin-like growth factors (IGFs).
Most data suggests that the primary dysfunction may be at the ovarian level or all manifestations of the syndrome may occur secondary to hyperinsulinemia [4].
The sign usually reflects abnormalities of the hormones that govern normal endometrial function. It may result from ovarian, hypothalamic, pituitary, and other metabolic disorders, and from the effects of certain drugs. It may also result from emotional or physical stress, due to sudden weight change, debilitating illness, or rigorous physical training [1].
Morbidities associated with chronic anovulation include hyperinsulinemia, insulin resistance and early onset of type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, osteoporosis and infertility [2]. We attempted to study the association of insulin resistance in 50 women with PCOS.

Materials & Method

This was a cross sectional study conducted among 50 women with PCOS between ages of 16 to 35 years attending outpatient department in PES Kuppam. The study protocol was approved by the institutional review board at the study institution, and written informed consent was obtained from all study participants. Detailed history, physical examination laboratory evaluation which included the fasting serum glucose, fasting serum insulin were performed. The patients were selected according to Rotterdam's criteria.

- Ovulatory dysfunction such as amenorrhea or oligomenorrhea.
- Clinical or biochemical evidence of hyperandrogenism.
- Polycystic ovarian morphology on ultrasound scan defined as 12 or more follicles in each ovary and increased ovarian volume of >10ml.

Inclusion Criteria: Women with PCOS meeting Rotterdam's criteria, no existing medical illness.(Hypothyroidism, Hyperprolactenimia, congenital adrenal hyperplasia, cushing syndrome, androgen secreting tumours, Diabetes mellitus) and Age 16-35 year.

Exclusion criteria: Pregnancy, Lactation, Menarche less than 2 years ago, Women on drugs known to cause abnormal uterine bleeding- hormonal contraceptives drugs known to produce hirsutism/ galactorrhea (e.g. corticosteroids, androgens, cyclosporine, minoxidil, phenytoin, diazoxide, Cimetidine, Histamine-receptor blockade, Methyldopa, etc).

Method of collection of data

The relevant investigations, fasting plasma glucose level and fasting plasma insulin level was done and insulin resistance is calculated by using the following method:
Homa (Homeostasis Model Assesment)

$$HOMA - IR = \frac{(\text{Fasting serum insulin } (\mu U/ml) \text{ x fasting plasma glucose (mmol/litre)}}{22.5.}$$

Values >2.5 were taken as compatible with significant insulin resistance

Method of Statistical Analysis

The results for each parameter (numbers and percentages) for discrete data and averaged (mean $\pm$ standard deviation) for continuous data are presented in Table and Figure. The proportions were compared using Chi-square test of significance.
Chi-Square (χ^2) test for (2 x 2 tables)

Group	Attribute Characteristic finding		Total
	Absent	Present	
Group 1	A	B	a+b
Group 2	C	D	c+d
Total	a+c	b+d	N

a, b, c, d are the observed numbers.
N is the Grand Total

$$\chi^2 \text{ with 1 DF} = \frac{N(ad - bc)^2}{(a+b)(c+d)(a+c)(b+d)}$$

DF=(r-1)*(c-1), where r=rows and c=columns
DF= Degrees of Freedom (Number of observation that are free to vary after certain Restriction have been placed on the data)
The student't' test was used to determine whether there was a statistical difference between groups in the parameters measured. In all the above test the "p" value of less than 0.05 was accepted as indicating statistical significance. Data analysis was carried out using Statistical Package for Social Science (SPSS, V 10.5) package.

Results

Table 1 shows the various demographic distribution among 50 PCOS patients. Most common age group presented with PCOS were between 25-29 years which accounts to 42% of study population. The other age groups were less than 20 years, 21-24, and more than 30years which were 14%, 36% and 8% respectively. Among the study population unmarried were 14 cases accounting for 28%. In our study there was no lean PCOS cases. We had normal and overweight individuals each accounting about 46%. Obese PCOS were only 4%. Table 1 also show the positive family history of PCOS among the study population accounting for 10% (n=5). The positive family history of diabetes is found in 18 cases accounting for 36%. PCOS cases had family history of both PCOS and Diabetes which accounts for about 6%.

Table1: Demographic data

Variable	n	%
Age		
<20 yrs	7	14.0%
20-24 yrs	18	36.0%
25-29 yrs	21	42.0%
>=30 yrs	4	8.0%
Marital Status		
Married	36	72.0%
Unmarried	14	28.0%
BMI		
Underweight(<18)	0	0
Normal(18-24)	23	46.0%
Over weight(25-29)	23	46.0%
Obese(>=30)	4	4.0%
Family history of DM and PCOS		
PCOS	5	10.0%
DM	18	36.0%
Both	3	6.0%

Most common presenting variable was oligomenorrhea accounting about (n=17)34%. The next common presenting variable was infertility accounting for (n=13) 26%. The other presenting variables were polymenorrhea(n=7) accounting for 14%, amenorrhea in (n=7) 14% and hirsutism and weight gain accounting for 6% each (Table 2).

Table 2: Descriptive statistics for basic clinical variables

Present Complaints	Frequency	Percent
Amenorrhea	7	14.0
Hirsutism	3	6.0
Infertility	13	26.0
Oligomenorrhea	17	34.0
Polymenorrhea	7	14.0
Weight Gain	3	6.0
Total	50	100.0

Prevalence of insulin resistance: Out of 50 PCOS cases 18 cases had significant insulin resistance accounting about 36%.

Table 3: Comparison of glycemic status among study population with and without insulin resistance

	Levels	Homa				Total
		<2.5		>=2.5		
		n	%	n	%	
Fasting Glucose	<105	32	78.0%	9	22.0%	41
	105-125	0	0.0%	9	100.0%	9
	>125	0	0.0%	0	0.0%	0
Fasting Insulin	<=17	31	81.6%	7	18.4%	38
	>17	1	8.3%	11	91.7%	12

	HOMA	N	Mean	SD	Min.	Max.	't' value	'p' value
Fasting Glucose	<2.5	32	87.91	8.851	68	102	46.284	<0.001
	>=2.5	18	106.28	9.712	89	120		
	Total	50	94.52	12.714	68	120		
Fasting Insulin	<2.5	32	9.541	4.9772	2.9	17.4	41.450	<0.001
	>=2.5	18	24.522	11.4438	9.3	46.5		
	Total	50	14.934	10.6712	2.9	46.5		

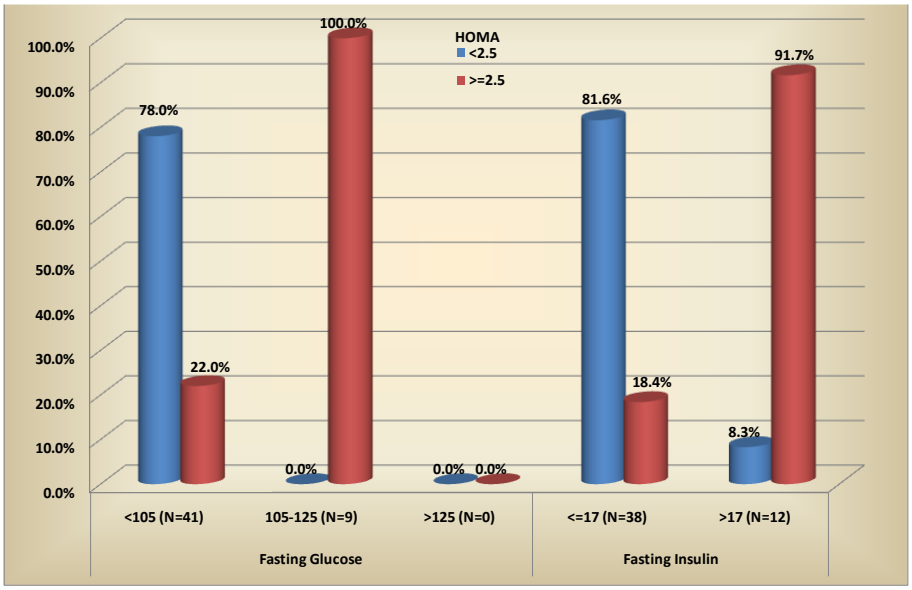

Fig 1: Distrinution of glycemic status per fasting glucose and fasting insulin levels.

This table shows the distribution of glycemic status and insulin levels among the study population. When we compared glycemic status and insulin resistance among the study population 9 cases with normal glycemic status had insulin resistance. All cases with impaired glycemic status had insulin resistance accounting (n=9) 100%.Among the study population 12 cases had increased fasting insulin levels in which 11 cases had insulin resistance accounting to 91.7%.

Table 4: Prevalence of insulin resistance in PCOS according to various basic clinical variables.

	Levels	Homa				Total	χ^2 value	'p' value
		<2.5		>=2.5				
		n	%	n	%			
BMI	Normal	17	73.9%	6	26.1%	23	3.719	0.156
	Overweight	14	60.9%	9	39.1%	23		
	Obese	1	25.0%	3	75.0%	4		
W:H Ratio	<=0.8	13	86.7%	2	13.3%	15	4.778	0.029
	>0.8	19	54.3%	16	45.7%	35		
Hirsutism	<8	29	76.3%	9	23.7%	38	10.424	0.001
	>=8	3	25.0%	9	75.0%	12		
Acanthosis	0	16	100.0%	0	.0%	16	35.903	<0.001
	1	12	100.0%	0	.0%	12		
	2	2	22.2%	7	77.8%	9		
	3	2	15.4%	11	84.6%	13		
Present Complaints	Amenorrhea	4	57.1%	3	42.9%	7	9.270	0.099
	Hirsutism	0	0.0%	3	100.0%	3		
	Infertility	11	84.6%	2	15.4%	13		
	Oligomenorrhea	11	64.7%	6	35.3%	17		
	Polymenorrhea	5	71.4%	2	28.6%	7		
	Weight Gain	1	33.3%	2	66.7%	3		

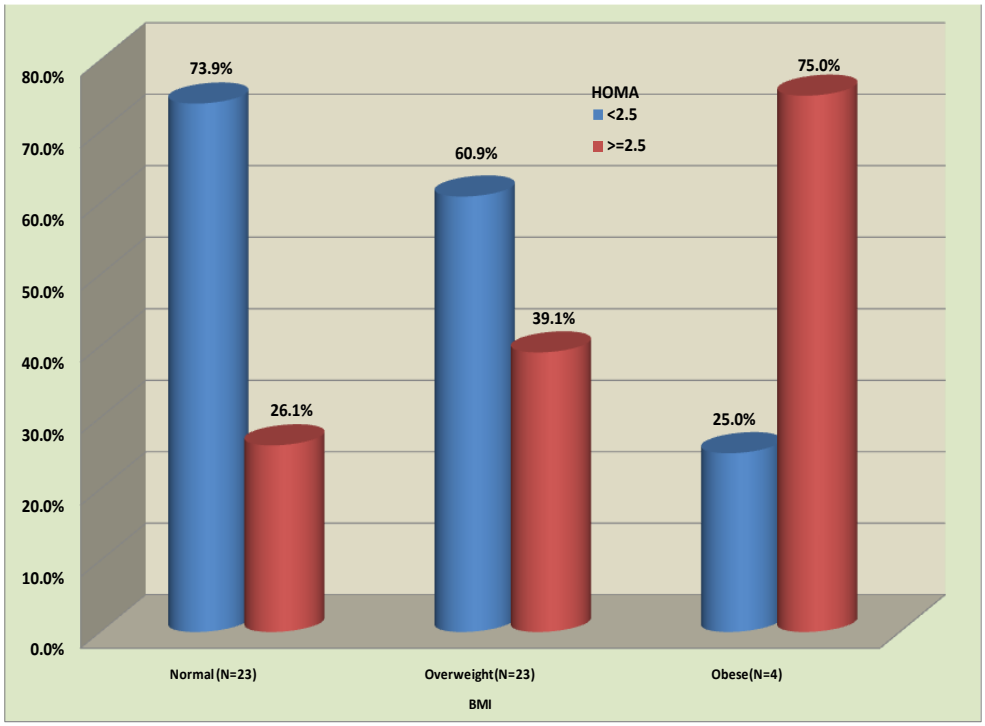

Fig 2: distribution of BMI according to insulin rsistance in PCOS

The relationship of insulin resistance with BMI and W:H ratio: About 35 individuals with W:H ratio of >0.8 had insulin resistance which accounts about 45.7%. 27 over weight cases had insulin resistance accounting for 39.1%. 23 cases with normal BMI had insulin resistance.

Association of insulin resistance with various clinical grading of hirsutism: Among 12 cases of clinically evident hirsute individuals 9 had insulin resistance which accounts about 75% and 9 of the clinically non hirsute individuals had insulin resistance accounting for 23.7%.

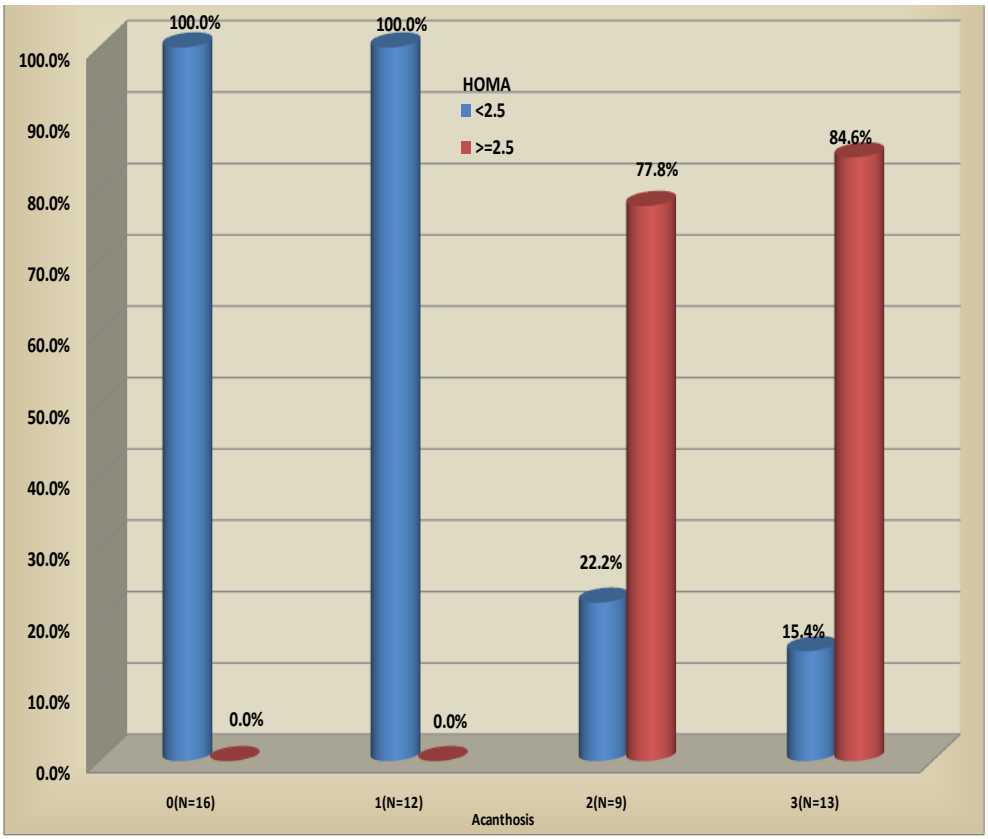

Fig 3: Distribution of Acanthosis according to insulin resistances in PCOS.

This bar diagram shows the prevalence of insulin resistance among cases with acanthosis. Among the study population insulin resistance was more prevalent in individuals with severe grading of acanthosis that is grade 2 and grade 3 accounting for 77.8% and 84.6% respectively.

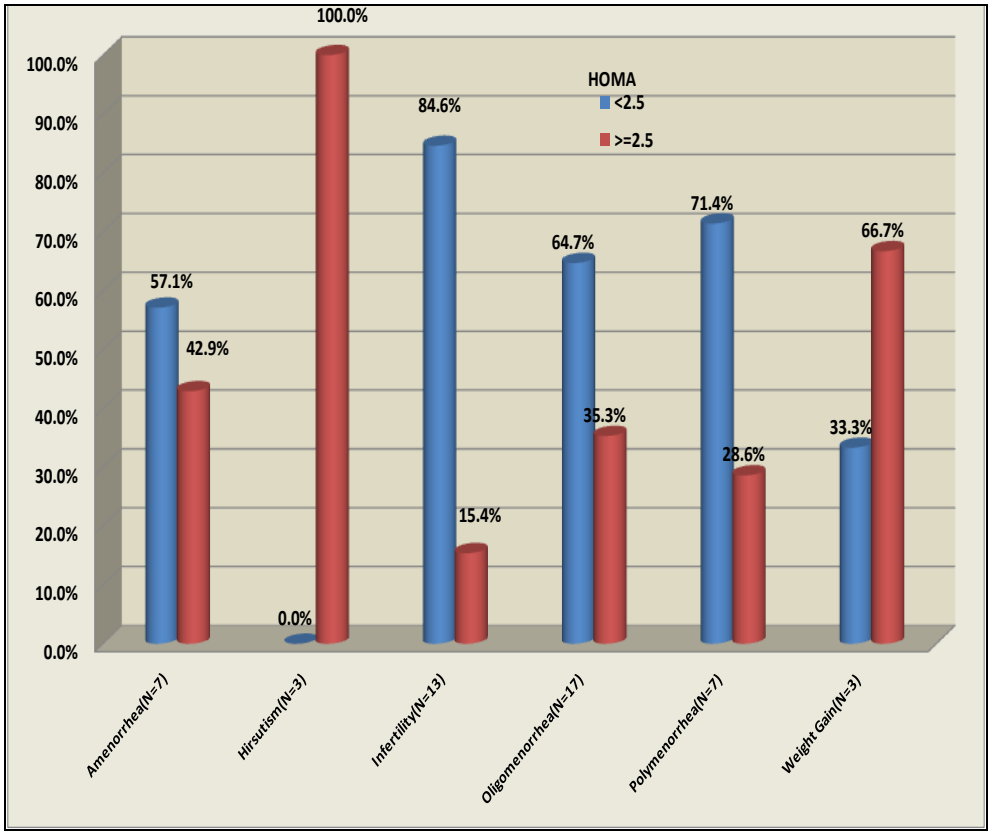

Fig 4: distribution of present complaints accrording to insulin resistance in PCOS.

This figure shows the various presenting symptoms among Study population. Most of the individuals with presenting complaints of menstrual disturbances had insulin resistance.

The menstrual disturbances were oligomenorrhea (35.3%), Polymenorrhea (28.6%) and amenorrhea (42.9%). The individuals with complaints of hirsutism were 3 and all had insulin resistance accounting for 100%. Among 3 individuals with weight gain 2 had insulin resistance accounting for 66.7%.

Discussion

Polycystic ovarian syndrome is a syndrome, not a disease, and reflects multiple potential etiologies and variable clinical presentations. Abnormal metabolic profiles in patients with PCOS are well documented in literature[4]. In this study we attempted to find the insulin resistance among the PCOS cases. In addition we tried to extrapolate the presenting clinical variables and glycemic status among the study population and their relation to insulin resistance [5].

Insulin resistance is defined as a reduced glucose response to a given amount of insulin. Resistance to insulin-stimulated glucose uptake is a relatively common phenomenon, but it is only one component of a condition referred to in the past as syndrome X, which is now called metabolic syndrome [6]. Various methods to measure the insulin resistance are euglycemic clamp method, in which an intravenous infusion of insulin which establishes a steady state of hyperinsulinemia is set up. A normal glucose level is maintained with an intravenous infusion of dextrose, and the point at which the glucose infusion rate equals glucose utilization is noted [7].

Homeostasis modular assessment and QUIKI are the other methods to determine insulin resistance. Among them HOMA which has been demonstrated to provide the best combination of sensitivity and specificity, as well as the best positive and negative predictive values as a screening test for predicting insulin resistance [8].

The prevalence of an isolated finding of polycystic ovaries (PCO) is dependent on age in of these woman, the prevalence being significantly higher in the younger age group (< 35 years) than among older women (> 36 years).

According to Clayton *et al.* study done in 1992 over 200 study population PCOS was found to be prevalent among age group between 16-24yrs. In our study also we found the mean age group to be 21-29yrs [9].

Regarding role of obesity in insulin resistance among PCOS approximately 50% of PCOS women are overweight or obese and most of them have the abdominal phenotype. Obesity, particularly the abdominal phenotype is responsible for insulin resistance and associated hyper insulinemia by increased estrogen production rate, increased activity of the opioid system of the hypothalamic-pituitary-adrenal axis thus resulting in decreased sex hormone binding globulin synthesis.

General consensus in the literature is that obese PCOS women are insulin resistant. A study by Ketel, Coen *et al* among 80 PCOS found obese women were more insulin resistant than normal-weight women (P = 0.001), and obese PCOS women were more resistant than obese controls (P=0.02).

Controversy remains as to the pathogenesis of the insulin resistance, and there are studies that suggest that obesity *per se* or increased central adiposity are responsible for the associated defects in insulin action [10]. Many of the conflicting studies can be explained by differing diagnostic criteria for PCOS and by the inclusion of both lean and obese women in the experimental sample. Studies conducted in United Kingdom strongly suggest that anovulation is associated with insulin resistance [11, 12].

According to Campbell *et al.*, higher triglycerides and lower HDL-cholesterol correlate with insulin sensitivity [13]. Strowitzki *et al.* demonstrated that reduced insulin sensitivity and dyslipidemia coexist in both obese and lean PCOS women [14]. Similar to these studies we also found that insulin resistance was found in over weight and PCOS with W:H ratio >0.8

corresponding to 39% and 45%. In our study group no insulin resistance was found in lean PCOS cases. The association of PCOS with insulin resistance, and the consequent increase in the risk for developing Type 2 DM and cardio vascular disease, has several important clinical implications. It indicates that PCOS is not only an infertility problem or a cosmetic annoyance, but it is foremost a general health problem. Therefore, any therapy for PCOS should optimally target not only the ovulatory dysfunction and hyperandrogenism but also the co-morbidities of the dysmetabolic syndrome associated with it. When evaluating women with PCOS, physicians should include assessments of glucose tolerance (via an oral glucose tolerance test), lipids, blood pressure, Long-term treatment of PCOS should focus not only on the conventional outcomes of regularization of menses and amelioration of hyperandrogenism, but should also attempt to prevent progression of metabolic abnormalities to type 2 diabetes and cardiovascular disease [101].

Legro *et al* prospectively studied 254 PCOS women, 40 % had glucose intolerance, 31% IGT and 7.5% type 2DM [15]. These rates were significantly higher than those for an age-, weight, and ethnicity comparable control population. In our study we found all the PCOS cases with impaired glucose tolerance had insulin resistance accounting to 100% [16].

Hirsutism is characterized by excessive growth of terminal hair in the androgen-sensitive skin regions. Chang *et al*. [1] and Dunaif *et al*. have demonstrated in those showed hirsutism also had some degree of decreased insulin sensitivity in both obese and non-obese women by different methods [17, 18]. But others have not been able to find any degree of insulin resistance in non-obese women with PCOS [19, 20].

More recently, some studies have suggested that there may be a link between insulin resistance and hirsutism rather than body weight in women with PCOS [21]. In our study we found 9 of PCOSs with significant hirsutism had insulin resistance. PCOS is one of the most common causes of anovulation and endocrine infertility in women [16]. Several studies have clearly demonstrated that menstrual abnormalities are more frequent in obese than normal-weight PCOS women [22].

In a prospective study by Gambineri *et al* carried out among 158 anovulatory women, the dose of clomiphene required to achieve ovulation was positively correlated with body weight.80 Administration of insulin sensitizing agents, such as metformin and troglitazone was in fact associated with improved menstrual cyclic pattern in women with PCOS.

Conclusion

Majority of the PCOS cases had normal or impaired glycemic status. All the cases with impaired glycemic status had positive insulin resistance. However 22% of those who had a normal glycemic status also showed insulin resistance. 75% of the cases with clinically evident features of insulin resistance like acanthosis, hirsutism and abdominal obesity exhibited positive HOMA ratio. Therefore all cases of PCOS with impaired glycemic status had insulin resistance and so by evaluating the glycemic status and other clinical parameters like hirsutism, acanthosis, abdominal obesity and menstrual irregularities we were able to arrive at the diagnosis of insulin resistance among study population. The study justifies the elaborate evaluation of metabolic and clinical parameters in patients with PCOS and may indicate that these women have a lowered metabolic clearance rate of insulin. Thus we could conclude that the routine investigations for insulin resistance were not mandatory as the tests were not cost effective.

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