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Hyperinsulinemia in Polycystic Ovary Syndrome

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Abstract

Background: *Polycystic ovary syndrome is one of the most common endocrinopathies affecting 4.7% of women in reproductive age group contribute to a major share of anovulatory infertility. It is more prevalent in South Asian Women than in Caucasians though it can prevail in women of any ethnicity. PCOS is associated with 75% of anovulatory infertility. Even if they conceive, they can have very high pregnancy loss rates. The primary defect in PCOS may be insulin resistance leading to hyperinsulinemia and abnormal glucose tolerance which is present in 60 – 70 % of PCOS women. Understanding the role of insulin resistance in PCOS has led to the successful use of insulin sensitizing drugs in the treatment of this syndrome.*

Objective: *To study the prevalence of hyperinsulinemia and abnormal glucose tolerance among women with PCOS and to study the relationship between hyperinsulinemia and abnormal glucose tolerance, obesity, hyperandrogenism, acanthosis nigricans, infertility, gonadotropin profile and ovarian ultrasound morphology.*

Materials and Methods: *It was conducted as a prospective observational study. All patients diagonised of PCOS based on the ESHRE – ROTTERDAM revised consensus 2003 were included in the study. Patients with hyperandrogenemia due to other causes were excluded. A detailed history, examinations, ultrasound, oral glucose tolerance test, fasting insulin etc were done. Data analysis was performed using SPSS 16.*

Results: *The prevalence of hyperinsulinemia among PCOS patients was found to be 47.7%.in PCOS women hyperinsulinemia patients were found to have higher BMI, FI and lower FBS: FI compared to non – hyperinsulinemia women.*

Conclusion: *PCOS has an increased prevalence among obese women. Many women with PCOS are likely to have hyperinsulinemia, the earliest marker of insulin resistance and increased central fat distribution.*

Keywords: *Polycystic Ovary Syndrome, obesity, hyperinsulinemia.*

Introduction

Polycystic ovary syndrome (PCOS) is heterogenous collection of signs and symptoms that when gathered together, form the spectrum of disorder with mild presentation in some and severe disturbances in others. The condition is now well recognized as having a major effect throughout life on the reproductive, metabolic and cardiovascular health of affected women from adolescence till old age.

PCOS can manifest at any age, ranging from childhood (premature puberty), teenage (hirsuitism, menstrual abnormalities, obesity), early adulthood (infertility, abnormal glucose tolerance) to later life (diabetes mellitus (DM) – 4 to 7 fold risk[12], hypertension and cardiovascular diseases[13]) and have psychological issues (impaired quality of life and increased anxiety and depression)[9]. On a long term, they are at increased risk to develop endometrial and breast cancer secondary to chronic an ovulation and hyperinsulinemia[10,11].

The current diagnostic criteria for PCOS is the 2003 Rotterdam ESHRE/ASRM revised consensus[14,15] according to which at least 2 of the following criteria are sufficient for the diagnosis: Chronic oligo/anovulation; Clinical and/or biochemical evidence of hyperandrogenism and appearance of polycystic ovaries on ultrasound, after excluding other aetiologies for anovulation and hyperandrogenism.

Although not included in the diagnostic criteria, a major feature of PCOS is insulin resistance leading to compensatory hyperinsulinemia (HI), acanthosis, hyperandrogenism, cardio metabolic risk, abnormal glucose tolerance and type 2 diabetes mellitus[16.]. it is postulated that women with PCOS have intrinsic insulin resistance(IR) distinct from obesity – associated IR[17]. Some evidence suggests that women with PCOS have a greater predisposition to obesity[18] which may aggravate PCOS – related intrinsic IR and associated reproductive[19] and metabolic disturbances[20,21,22,23].

There is increasing focus on the complications associated with metabolic disturbances among women with PCOS. Risk factors for DM2 and CVD in PCOS include IR, obesity especially abdominal obesity, dyslipidemia, inflammation and elevations in circulating proteins thought to lead to vascular damage. PCOS women are also proposed to have a more rapid conversion from IGT to DM2[24]. Women with PCOS have an elevated prevalence of the metabolic syndrome[25, 26,27] thus making them high risk for DM2 and CVD[28,29,30]. Disturbingly, even adolescents with PCOS commonly have IGT, DM2, and the metabolic syndrome, suggesting an adverse contribution of PCOS to metabolic health across the female lifespan[31, 32].

Insulin – sensitizing agents (Metformin and Thiazolidenediones (TZDs) have been recently proposed as the therapy of choice for PCOS, since insulin resistance and associated hyperinsulinemia are recognized as important pathogenic factors of the syndrome[33]. Several trials have been conducted to assess the effects of these drugs on insulin resistance and other aspects of this multifactorial disease. However most had a low sample size, short follow up period or used additional treatments with gonadotropins or ovulation inducing agents which can yield altered results. Hence no definite statement has been made yet for clinical practise[34].

In the last 2 decades, insulin sensitizers have been persistently trialed in PCOS with encouraging results and Metformin has been the most widely used and best studied agent. Metformin, an oral hypoglycaemic agent – a biguanide, approved and accepted widely as one of the first line drugs for type 2 diabetes mellitus[35]. Metformin is associated with significantly less side – effect profile than the other drugs, effective in ameliorating reproductive abnormalities (restore ovulation and regularize menses, increase pregnancy rates, decrease early pregnancy loss, does not produce ovarian hyperstimulation or multiple pregnancies) and reducing androgen production as well as improving glucose, insulin, lipid profiles and pro – inflammatory cytokines.

Given the increasing prevalence of obesity, infertility, hirsuitism and PCOS, we considered it worthwhile to study the disease profile in our population.

Material and Methods

This study was conducted as a prospective observational study. It included 65 patients diagnosed with PCOS based in the ESHRE – Rotterdam revised consensus 2003.

Inclusion Criteria: Women in the age of 15 – 35 yrs with complaints of either of the following.

- Menstrual irregularity
- Signs of Hyperandrogenism
- Obesity
- Infertility
- Already diagnosed cases of PCOS by Ultrasound.

Exclusion Criteria:

- Patients with hyperandrogenemia secondary to ovarian or adrenal neoplasms, Cushing's syndrome, late onset congenital

adrenal hyperplasia or drug induce hyperandrogenism.

- Patients with other recognizable form of oligo/anovulation like hypothyroidism, Hyperprolactinaemia, ec
- Patients unfit for Metformin therapy like patients with hepatic or renal dysfunction or cardiovascular disease.

A detailed history and physical examination were done. Anthropometric parameters like weight, height, BMI, waist and hip circumference and waist to hip ratio were measured. Hirsuitism was assessed using the modified Ferriman – Gallwey scoring system.

Examination was followed by a baseline pelvic ultrasound. A transabdominal pelvic ultrasono-graphy was carried out in the follicular phase using a 3.5 MHz probe on Sonaline Versa model (Siemens, Germany) in unmarried women and a transvaginal pelvic ultrasound using a 6.5 MHz probe of the same machine in married women. Ovarian volume (0.523 x length x width x thickness) and number of follicles in each ovary were noted. The mean values were obtained by adding values of both the ovaries and then dividing by two. An ovary was diagnosed as being polycystic if the ovarian volume was > 10 cc if it contained > 12 follicles.

For estimation of oral glucose tolerance test (OGTT), patients were instructed to have carbohydrate diet of at least 300g for 3 days prior to the test. After an overnight fasting, basal venous blood sample was taken. Blood samples were again obtained at 120 min after 75g of glucose loading for glucose estimation. World Health Organization (WHO, 1999) criteria was used for interpretation. FBS values in between 10 – 126 mg% and 2hr post – glucose values between 140 – 199 mg% indicated impaired glucose tolerance while FBS > 126 mg% or PGBS > 200mg% indicated frank diabetes mellitus.

Fasting Insulin was tested for and Fasting Blood Sugar to Fasting Insulin (FBS: FI) ratio was also calculated. FBS:FI < 4.5 or fasting insulin of > 20 uIU/ml was considered consistent with insulin resistance. FBS: FI ratio is an easily obtainable, safe, highly sensitive, and specific measure of insulin sensitivity. The predictive power of both a positive and a negative test is excellent.

Venous blood sample was taken on day 2 of menstrual cycle for estimation of follicle stimulating hormone (FSH), lutenising hormone (LH) and LH to FSH ratio was calculated and values > 2 was considered as indicative of elevated LH:FSH.

This was followed by a targeted laboratory assessment which included the measurement of basal 17 alpha hydroxyl progesterone level in the follicular phase of the cycle to exclude adult onset congenital adrenal hyperplasia, and TSH to exclude thyroid dysfunction and serum prolactin in patients with galactorrhoea to rule out hyperprolactinemia.

Data analysis was performed using SPSS 16 with advanced statistical programme. To test the statistical significance of the association between risk factor and the problem under consideration chi – square test with correction factor was applied. To test the statistical significance of the difference in mean values between 2 groups, student's t test was applied.

Results

A total of 65 cases with evidence of chronic oligo or anovulation, obesity, hyperandr-ogenism, and or infertility were analysed. 46.2% belonged to the 20 – 25 year age group.

Table 1 Distribution of patients according to BMI

Category	BMI (in kg/m^2)	Frequency	Percent
Lean	<18.5	3	4.6
Normal	18.5 – 24.99	26	40.0
Overweight	25 – 29.99	28	43.1
Obese	> 30	8	12.3

43.1% belonged to the overweight category. 12.6% were frankly obese. 35 patients (53.8%) had an abnormal Waist to Hip ratio of >= 0.85.

Table 2 Distribution according to menstrual pattern

Mentioned Pattern	Frequency	Percentage
Regular	6	9.2
Oligomenorroea	52	80.1
Secondary Amenorrhoea	3	4.6
Polymenorrhoea	4	6.2

Prevalence of infertility in the study group was 57.14%.

Table 3 Distribution of patients according to hirsuitism

Modified Ferriman – Gallwey score(MFGS)	Category	Frequency (n)	Percentage (%)
<8	No significant hirsuitism	7	10.8
8 – 13	Mild Hirsuitism	34	52.3
14 – 23	Moderate Hirsuitism	24	36.9
>=24	Severe Hirsuitism	0	0

42% patients did manifest acne as one of the evidence of hyperandrogenemia. 69.2% patients were associated with a positive family history of Diabetes among first degree relatives

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Table 4 Distribution of patients according to Fasting Insulin levels, FBS:FI ration, FSH:LH ratio, Glucose tolerance test

Parameter		Frequency	%
Fasting insulin	Non – hyperinsulinemia (FI < 20 uIU/ml)	34	52.3
	Hyperinsulinemia (FI > 20 uIU/ml)	31	47.7
FBS : Fasting insulin ratio	Non – insulin resistant	37	56.9
	Insulin resistant (<4.5)	28	43.1
Glucose tolerance	Normal	44	67.7
	Impaired	19	29.2
	DM	2	3.1
LH:FSH ratio	Normal	36	55.4
	Abnormal	29	44.6

Acanthosis as a clinical marker hyperinsulinemia was seen in 29.2% cases (19 patients). Of these 19 patients with acanthosis, 17 were hyperinsulinemic.

Table 5 Distribution of patients according to Ovarian ultrasound findings.

Ultrasound parameter		Frequency	%
Ovarian volume	< 10cc	3	4.6
	> 10cc	62	95.4
Antral Follicle Count	< 12	32	49.2
	= > 12	33	50.8

Table 6 Comparison of Mean values between Hyperinsulinemic & Non hyperinsulinemic PCOS

	Non – Hyperinsulinemic (N = 34) (mean+SD/%)	Hyperinsulinemic (N = 31) (mean+SD/%)	T	P
BMI	24.2 + 3.6	26.9 + 3.8	-3.054	0.003
WAIST CIRCUMFERANCE	29.8 + 4.3	32.2 + 3.8	-2.349	0.022
W:H	0.9 + 0.1	0.9 + 0.1	-1.812	0.075
MENSES/YR	7.2 + 4.0	6.8 + 3.6	0.431	0.668
CYCLE LENGTH	66.7 + 37.8	64.7 + 29.1	0.237	0.813
Mod.FG SCORE	11.7 + 3.1	13.3 + 4.1	-1.737	0.087
FASTING INSULIN (FI)	16.1 + 2.4	25.6 + 4.1	-11.58	0.000
FBS:FI	5.9 + 1.2	3.9 + 0.7	7.792	0.000
FBS	92.6 + 9.6	99.0 + 13.9	-2.160	0.035
2HrPPBS	126.9 + 22.1	137.2 + 17.2	-2.084	0.041
LH	11.1 + 7.3	7.9 + 3.8	2.165	0.034
LH:FSH	2.6 + 1.6	1.9 + 1.0	2.085	0.041
OVARIAN FOLLICULAR NO	12.5 + 1.7	11.7 + 2.3	1.500	0.139
OVARIAN VOL.	13.5 + 3.2	12.8 + 2.5	0.986	0.328
			X^2	P
IRREGULAR CYCLES	85.3%	96.8%	2.551	0.110
INFERTILITY	32.4%	29.0%	7.042	0.030
F/H OF DM	67.6%	71.0%	0.084	0.772
HIRSUITISM	79.4%	93.5%	2.717	0.099
ACNE	32.4%	51.6%	2.477	0.116
ACANTHOSIS	5.9%	51.6%	16.935	0.000
PCO BY USG	100.0%	96.8%	1.114	0.291
IMPAIRED GLUCOSE TOLERANCE	14.7%	51.6%	10.100	0.001

Discussions

PCOS is one of the most common endocrinopathies affecting 4.7% of women in reproductive age group and contribute to a major share of anovulatory infertility [1]. In one series 46.2% belonged to the 20. 25 year age group. In a study by Pier point et al, mean age of presentation was 26.4 years[2]. 43.1% cases in our series belonged to the overweight category (BMI 25 – 29.99 kg/m^2).

In our study obese PCOS patients were found to be associated more with menstrual disturbances than non obese, which was also found to be statistically significant with a p value < 0.05. also a significant negative co – relation was observed between BMI and number of menstrual cycles per year with a co – relation co – efficient r - -0.3, p<0.05.

Also a strong positive co – relation was observed between BMI and mod. Ferriman Gallwey scores with a co – relation co – efficient r=0.5, p<0.05 indicating the strong association between obesity and hyperandrogenism and therefore the high prevalence rates of hirsuitism among obese PCOS patients.

Balen et al observed that obesity was significantly associated with increased risk of hirsuitism, raised serum testosterone, menstrual cycle disturbances and infertility[3].

In our series, 90.8% patients presented with irregular menstrual bleeding and 80.1% had oligomenorrhoea. Aruna et al reported irregular cycles in 80.5% PCOS and oligomenorrhoea in 63.5% [4]

The prevalence of infertility in this series was 57.14%. Goldzieher et al reported a prevalence of 74% for infertility among 1079 PCOS subjects studied by them [5].

89.2% of our study subjects manifested hirsuitism. Aziz et al found a prevalence of 72% for hirsuitism in their study as 716 Caucasian PCOS women [6].

95.4% cases had an ovarian volume of more than 10cc. The actual number of follicles has been shown to be of less relevance than the volume of ovarian stroma or of the ovary itself, which has been shown to closely correlate with serum

testosterone concentrations and hyperandrogenism [7].

44.6% of PCOS patients were found to have elevated LH:FSH ratio.

A significant positive co – relation was observed in our study between serum lutenising hormone levels and ovarian volume with a co – relation co – efficient r=0.4, p<0.05 indicating that the excess secretion of LH leads to stroma hyperplasia in polycystic ovaries. Balen et al had observed that ovarian volume were found to be significantly correlated with high serum LH and serum testosterone levels.

The prevalence of hyperinsulinemic in our series was 47.7%. The mean values of serum FI was 20.7 + 5.9uIU and is comparable to other reports [8].

When PCOS women were classified based on their fasting insulin levels hyperinsulinemic women were found to have higher BMI, FI AND lower FBS:FI compared in non hyperinsulinemic women.

Fasting plasma glucose to fasting insulin ratio is a good measure of insulin sensitivity in PCOS women and has both high sensitivity and specificity for detecting insulin resistant women. Considering this as the parameter for insulin sensitivity and the cut off as a ratio < 4.5[187], the prevalence of insulin resistance (IR) was found to be 43.1% in the study.

Out of 65 patients, 21 (32.3%) had abnormal glucose tolerance. 19 had impaired glucose tolerance while 2 patients (3%) had overt diabetes mellitus (DM). Hence the prevalence of impaired glucose tolerance (IGT) amongst PCOS patients was found to be 29.2%. Out of 21 PCOS women with abnormal glucose tolerance, 14 were obese and 7 non – obese showing that obesity seems to be twice as prevalent among glucose intolerant PCOS women. Of the 2 women with overt diabetes, both had elevated waist: hip ratio (WHR) and one was obese (BMI = 32) and another overweight (BMI = 28). The mean values of FBS and PPBS noted were 95.4 + 12.4 and 132.1 + 21.0mg% respectively.

Various studies have shown that 30 – 40% of women with PCOS have IGT and as many as 10% develop T2DM by their fourth decade of life [9,10,11]. Incidence of IGT in general population was 1.3%, that of conversion from IGT to DM was 3% [12].

Our study group comprised of a much younger PCOS population and yet showed 29.2% and 3% prevalence rate for IGT and DM respectively thus highlighting the need for early screening and diagnosis of IGT and DM in PCOS women. Supporting this finding is the recent recommendation by the Androgen excess PCOS society[13], recommending screening of all women with PCOS for IGT with a 2 hour OGTT; to be repeated every 2 years even if normal or earlier if any other risk factor appears; and annually for PCOS with IGT to check for development of T2DM.

Conclusion

- Polycystic ovary syndrome has an increased prevalence amongst obese women. Many women with PCOS are likely to have hyperinsulinemia, the earliest marker of insulin resistance and increased central fat distribution.
- There is a strong association between hyperinsulinemia and central or visceral obesity, acanthosis, abnormal glucose tolerance and hirsuitism; acanthosis being the clinical manifestation of insulin resistance and hirsuitism reflecting the hyperandrogenemia mediated by hyperinsulinemia.
- Young obese PCOS women are likely to be anovulatory and should be investigated for hyperinsulinemia.
- Hyperinsulinemia being the earliest manifestation of insulin resistance mandates early detection and management interventions to avoid further progress of this syndrome to various complications observed such as impaired glucose

tolerance, type 2 diabetes mellitus, hyperandrogenism and infertility.

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