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COMPARISON OF INSULIN RESISTANCE BETWEEN NON-OBESE AND OBESE POLYCYSTIC OVARIAN SYNDROME

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Abstract

Background: The etiology of Polycystic ovarian syndrome (PCOS) remains unknown and it is believed that there may be several different pathways leading to the syndrome PCOS is associated with peripheral insulin resistance and hyperinsulinemia, and the degree of both abnormalities is amplified by the presence of obesity. Studies of insulin-mediated glucose disposal have shown that women with PCOS have peripheral insulin resistance similar in magnitude to that seen in patients with non-insulin-dependent diabetes mellitus (NIDDM). **Aim**: To evaluate for insulin resistance in PCOS patients in obese and non obese patients. **Materials and methods**: The present study includes 80 women clinically diagnosed with PCOS within the age group of 18-40 years. **Results**: This study shows that most of the women with PCOS have heritable form of insulin resistance, and prevalence of insulin resistance is twofold higher in obese compared to non-obese PCOS. **Conclusion**: Presence of obesity adds to insulin resistance. Hence women diagnosed have PCOS should be evaluated for insulin resistance specifically if they are obese.

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1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among women of reproductive age, the prevalence being 5-10%. Between 1 in 10 and 1 in 20 women of childbearing age has PCOS. It can occur in girls as young as 11 years old. PCOS is characterized by anovulation and hyperandrogenism. Anovulation presents as menstrual disturbances, oligomenorrhea or amenorrhea. Hyperandrogenism may manifest itself as symptoms of clinical hirsutism, acne, androgenic alopecia, or as biochemical hyperandrogenism, elevated serum testosterone and/or androstenedione levels [1]. The association between bilateral polycystic ovaries and amenorrhea, oligomenorrhea, infertility, hirsutism and obesity was first described in 1935 by Stein and Leventhal.

Obesity is a common feature of PCOS, as is insulin resistance, which is frequently found even in lean women with PCOS [2,3,4]. Typically, women with PCOS have increased levels of serum testosterone and Luetinizing hormone (LH), and decreased levels of FSH, sex hormone-binding globulin (SHBG) and increased LH/FSH which correlate with hyperinsulinemia and obesity [5].

Polycystic ovaries detected by ultrasonography are frequently noted in women with PCOS but also in about 20% of women who consider themselves healthy. The detection of PCOS is not simple, as the syndrome is associated with multiple clinical presentations. The most recent recommendation for the diagnostic criteria of PCOS is as two out of three of (1) oligo and/or an ovulation, (2) clinical and/or biochemical signs of hyperandrogenism, and (3) polycystic ovaries, when other etiologies such as congenital adrenal hyperplasia, secreting tumors and Cushing's syndrome have been excluded.

Many PCOS women have a heritable form of insulin resistance, independent of obesity. Hyperinsulinemia is caused by insulin resistance resulting in ovarian hyperandrogenism which manifests like seborrhea, acne, hirsutism and androgenic scalp alopecia. The cause and effect relationship between hyperinsulinemia and hyperandrogenism is best exemplified in subjects of hyperandrogenism, insulin resistance and acanthosis nigricans (HAIRAN) syndrome. At puberty, LH secretion rises. The combination of severe IR and LH stimulation results in hypersecretion of testosterone by the ovary [6,7].

Android obesity is distribution of fat in abdomen (apple shape), Gynoid obesity is where fat deposited mainly on the hips and

thighs (pear shape). Specifically android obesity is common in PCOS. Obesity enhances the features of insulin resistance and is associated with reproductive dysfunction, including menstrual irregularity, infertility and complications during pregnancy. Obesity, especially android obesity worsens the clinical features of menstrual irregularity and infertility. Obesity is also correlated serum androgens and leutinizing hormone in PCOS [8,9].

Insulin resistance and compensatory hyperinsulinemia are associated with raised plasma triglycerides, low density lipoproteins, very low density lipoproteins and reduced high density lipoprotein cholesterol concentrations, high blood pressure and increased risk of developing type 2 diabetes mellitus. Hyperinsulinemia may be directly related to its deleterious effects. This clustering of haemodynamic and metabolic abnormalities is associated with a significant increase in the risk of coronary heart disease, cerebrovascular disease and peripheral vascular disease.

Treatment of insulin resistance can reduce ovarian androgen secretion and can cause resumption of ovulatory menstrual cycles, suggesting that there is a cause and effect relationship between insulin resistance, hyperandrogenism and anovulation, an insulin sensitizer, lowers the circulating androgens by lowering insulin levels and induces ovulation. It also improves the clinical and biochemical features of PCOS and decreases the risk endometrial and breast malignancies, cardiovascular and cerebrovascular diseases [9,10].

Aim of this study is to know prevalence of insulin resistance in non-obese and obese PCOS and analyze the prevalence of infertility, menstrual irregularities and clinical hyperandrogenism in non-obese and obese.

Data on prevalence of PCOS are variable, in part because of lack of international consensus on diagnostic criteria of PCOS. The prevalence of polycystic ovaries (PCO) in the general population has been studied widely but only a few investigators have taken up the challenge to study the prevalence of the syndrome. Hence this study was conducted in women diagnosed to have PCOS should be evaluated for insulin resistance.

2. MATERIALS AND METHODS

The present study included 80 patients diagnosed as polycystic ovarian syndrome who were reproductive age group of females 18-40 yrs attending outpatient department of obstetrics and gynecology, Niloufer Hospital.

Inclusion criteria: Patients who were diagnosed to have PCOS according to Rotterdam criteria were included they are as follows:

- Oligo or anovulation (fewer than six menstrual periods in the preceding year).
- Clinical and/or Bio-chemical evidence (total Testosterone >/= 0 .6 ng/ml) of Hyperandrogenism.
- Polycystic ovaries. Presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and/ or increased ovarian volume (> 10 ml).

PCOS was defined when at least two of the above features were present after exclusion of other etiologies (Rotterdam criteria)

Exclusion criteria: H/O of Endocrinal disorders, H/O of Diabetes Mellitus, H/O of Liver Disorders, H/O of thyroid and Renal abnormalities, and also current or previous (within the last months) use of oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents, anti diabetic, anti obesity drugs, sodium valproate, aspirin, statins and other hormonal drugs.

For the patients selected for study included blood samples were obtained in the morning between 0800 and 0900 hours after overnight fasting. Blood samples were collected during early follicular phase (day 2 to 5) of a menstrual cycle.

Fasting glucose levels are obtained by glucose oxidase method

Fasting insulin was determined by double anti body RIA

For all non-obese and obese PCOS fasting glucose, fasting Insulin, LH, FSH and TSH are done Basic investigations like blood sugar, blood urea, serum creatinine, serum bilirubin, serum ALT and serum electrolytes were done to rule out Diabetes Mellitus, Liver and Renal disease.

Informed consent was obtained from all subjects after explanation of the nature and purpose of the study and also approved by ethics committee. A detailed history regarding menstrual irregularities, hirsutism, acne, weight gain, reproductive function, use of meditations including O.C. pills, and also family history of PCOS, diabetes mellitus was taken.

Obese and non obesity were divided based on BMI >30 kg/m2 and waist/hip ratio above 0.85. So Height is measured bare foot to the nearest 0.5 Cm. On a wall mounted Harpenden standiometer. Weight was measured to the nearest 0.5 Kg. Body mass Index (BMI), a measure of relative obesity was calculated as a mathematical function of weight and height. Waist and hip

circumference (in centimeters) were measured in duplicate with an inelastic tape at midway between lowest part of the ribcage and highest point on iliac crest and maximum diameter respectively. The waist/hip ratio was calculated as waist circumference divided by hip circumference was noted.

The presence of hirsutism was noted in every woman quantitating the presence of terminal hairs over nine body areas (i.e. upper lip, chin, chest, upper and lower abdomen, upper and lower back, upper arm and things). The presence or absence of acne, androgenic alopecia, acanthosi nigricans was recorded.

Transabdominal ultrasonography was performed for all patients to diagnose polycystic ovaries using curvilinear transducer with frequency 3.5 mega hertz.

For Assessing IR:

After estimation of fasting insulin, the IR is accessed by most commonly used simple method for confirmation of IR by fasting glucose to fasting insulin ratio FG/FI add to group, FG/FI ratio < 4.5 is considered of IR. In this study FG/FI ratio < 4.5 is considered as IR. Taking FG/FI < 4.5 as insulin resistant decision for planning mode of treatment is made.

3. RESULTS

In this study, 80 cases diagnosed as PCOS according to Rotterdam criteria including non-obese and obese PCOS are taken. The following features are studied and the analysis of the results.

TABLE 1: Age among non obese and obese PCOS

Age Distribution among non-obese & obese PCOS					
S.No	Age	Non Obese PCOS		Obese PCOS	
		No.	%	No.	%
1	< 19 Yrs	9	22.50%	8	20%
2	20-24 Yrs	21	52.50%	12	30%
3	25-29 Yrs	8	20%	12	30%
4	> 30 Yrs	2	5%	8	20%

TABLE: 2 Socio economic status among non obese and obese PCOS

		Non Obese PCOS		Obese PCOS	
S.No	Range	No.	%	No.	%
1	Low	2	5%	9	22.50%
2	Middle	37	92.50%	29	72.50%
3	High	1	2.50%	2	5%

TABLE 3: Complaints among non obese and obese PCOS.

S.No.	Complaint	Non Obese PCOS		Obese PCOS	
		No.	%	No.	%
1	Infertility	17	42.50%	22	55%
2	Irregular menstrual cycle	20	50	10	25%
3	Others	3	7.50%	8	20%

TABLE 4: Family history of Diabetes mellitus

S.No.	H/O Diabetes Mellitus	Non Obese PCOS	Obese PCOS
1	Mother	7	4
2	Father	4	11
3	Siblings	1	2

TABLE 5: Clinical hyperandrogenism

S.No.	Clinical Manifestation	Non-Obese	Obese
		PCOS	POS
1	Acne	17	19
2	Hirsuitism	28	32
3	Scalp Alopecia	6	5
4	Acanthosis nigricans	4	17

TABLE 6: Insulin resistance in non obese and obese PCOS

		Non Obese		Obese PCOS	
		No.	%	No.	%
1	Insulin Sensitive	27	67.50%	12	30%
2	Insulin Resistant	13	32.50%	28	70%

4. DISCUSSION

Polycystic ovarian syndrome is now recognized as not only a reproductive disorder but also a metabolic syndrome with long term effects on women's health. Prevalence of age and socioeconomic status is shown in table-1&2 indicate no correlation with age groups but more seen in socioeconomic status belonging to middle class.

Infertility is more prevalent to obese PCOS than Non-obese PCOS. Prevalence of infertility in PCOS in this study is 48.75% (table-3) which is correlated with other studies as Franks 42% [11], Goldzeiher and green series 64% [12]. Prevalence of infertility in this study in non-obese PCOS is 42.5% and obese PCOS is 55% which is matching with NCBI series in non-obese PCOS 37.8% and in obese PCOS is 38.9%. Study shows that probability of occurrence of infertility in PCOS is statistically significant chi square test is 6.25 (P value < 0.04).

Obesity, insulin resistance and strong family history of Diabetes mellitus are common features of PCOS. In the present study, prevalence of family H/O Diabetes is non-obese PCOS is 30% and in obese PCOS is 42.5% (table-4and figure-1) Prevalence of Acne in this study is 45% (table-5 and figure-2) which is comparable to studies done by Franks is 37% [11] and conway series is 24% [13]. Hirsuitism in present study is 75% which is correlating with other studies Franks series (64%), Conway et al (61%) and Goldzehier and green (69%). Hirsuitism in PCOS typically begins in adolescence and progresses with age. So this study shows that simple reassurance is not appropriate for most of the women with hirsuitism.

Over all prevalence of insulin resistance in this study is 51.25% which is comparable with study done by Lippincott William Obst and gynaecological survey (50-70%). Study show (table-6 and figure-3) prevalence of insulin resistance in non-obese PCOS is 32.5% and in obese PCOS is 70% which is in accordance with study conducted by curropin obstt gynaecol study (non-obese PCOS 30% and in obese PCOS is 75%).

Statistical analysis of this study has shown that probability of occurrence of insulin resistance in PCOS is significant (chi square 11.26 P value < 0.00079).

This study shows that most of the women with PCOS have heritable form of insulin resistance, and prevalence of insulin resistance is twofold higher in obese PCOS compared to non-obese PCOS.

Thus this evidence supports link between hyperinsulinemia and clinical features of PCOS. Hence all women diagnosed to have PCOS must be advised measures like weight loss, exercise and drugs like Metformin, Diazoxide and Troglitazone. This helps to improve fertility and also decreases the occurrence of late sequelae like Diabetes Mellitus, cardiovascular disease, Hypertension and endometrial carcinoma. Thus all women diagnosed to have PCOS should be evaluated for insulin resistance.

CONCLUSION

Prevalence of infertility is more in obese compared to non-obese PCOS. Hence all patients presenting with complaint of infertility should be evaluated to diagnose PCOS. Hallmark feature of PCOS is menstrual irregularities, which occur from the onset of puberty. Hirsutism in PCOS typically begins with adolescence and progresses with age. Insulin resistance is twofold higher in obese PCOS compared to non-obese PCOS. Hence presence of obesity adds to insulin resistance. So, all women diagnosed to have PCOS should be evaluated for insulin resistance specifically if they are obese.

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