

POLYCYSTIC OVARIAN SYNDROME AND HYPERINSULINAEMIA

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ABSTRACT

OBJECTIVE: To determine the occurrence of hyperinsulinaemia in women with polycystic ovarian syndrome (PCOS).

DESIGN: A descriptive study.

SETTING: Isra University Hospital, Hyderabad from January 2002 to December 2003.

METHODS: Total 64 subjects were recruited from gynaecological outpatients department, between the ages of 15 and 40 years with clinical diagnosis of polycystic ovarian syndrome, presenting with weight gain, oligomenorrhoea, secondary amenorrhoea, hirsutism or infertility and either ultrasound evidence of PCOS or raised Leutinizing Hormone (LH)/ Follicular Stimulating Hormone (FSH) ratio. Patient's venous blood was checked for fasting serum insulin.

RESULTS: Out of total 64 women selected, 37(57.81%) were between 21 – 30 years of age. Weight gain was the commonest presenting complain (84.37%) followed by oligomenorrhoea (79.68%). Infertility was found in 46 women (71.87%) and hyperandrogenism was observed in 43 women (62.49%). Thirty-nine women (60.93%) had ultrasound evidence of PCOS and 43 (67.18%) had LH / FSH ratio greater than 2:1. Hyperinsulinaemia was seen in 27 (42.19%) women.

CONCLUSION: In this study, 27 women (42.19%) had hyperinsulinaemia which indicates significant insulin resistance. Thus, all the patients presenting with clinical or biochemical evidence of PCOS must undergo checking of fasting serum insulin levels.

KEY WORDS: Polycystic ovarian syndrome. Hyperinsulinaemia. Insulin resistance.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) has a controversial definition. 1990 NIH diagnostic criteria have used a working definition that a patient must have ovulatory dysfunction and evidence of hyperandrogenism clinically or by laboratory means, but no other cause of hyperandrogenism.^{1,2} It is also defined as a heterogenous disorder which may present at one end of the spectrum, with the single finding of polycystic ovarian morphology as detected by pelvic ultrasound. At the other end of the spectrum, symptoms such as obesity, hyperandrogenism, menstrual cycle disturbances and infertility may occur either singly or in combination.^{3,4} 2003 Rotterdam diagnostic criteria have included the presence of two out of three manifestations for the diagnosis of PCOS i.e. irregular or absent ovulation, clinical and / or biochemical hyperandrogenism and / or polycystic ovaries on ultrasound.^{5,6} Thus, it is chiefly a diagnosis of exclusion.⁷ Most reporters suggest that the condition affects between 5 and 10 percent of women of reproductive age.⁸ It is the most common endocrinological condition observed from premenstrual to perimenopausal age. Unfortunately, its exact etiology remains still uncertain^{3,9,10} and from time to time hypothalamus, pituitary, adrenals and ovaries have been held responsible to be the causal

factor, alone or together. Lately, insulin resistance leading to hyperinsulinaemia¹¹ and excessive leptin secretion have been associated with PCOS, but the role of leptin causing PCOS is inconclusive.¹² A significant proportion of obese women with PCOS have greater insulin resistance than normal women. PCOS with hyperinsulinaemia is an established risk factor for non-insulin dependent diabetes, hypertension, dyslipidemia and cardiovascular disease, collectively known as metabolic syndrome or syndrome X. Thus, detection of insulin resistance in PCOS may assist in planning optimal treatments for anovulatory infertility and hyperandrogenaemia.¹³⁻¹⁵ Historically, the first report of a link between hyperandrogenism and metabolic defect was published in 1921, when Achard and Thiers described diabetes in bearded women.¹⁶ Later in 1935, Stein and Leventhal reported a series of seven women with bilateral polycystic ovaries and thickened ovarian cortex accompanied by amenorrhoea, hirsutism and infertility, but with no clear emphasis on the etiology of the disorder.¹⁷ It has become recognized increasingly that PCOS and insulin resistance are intimately related with respect to pathogenesis, endocrinal disturbances and molecular biology.³ The relative hyperinsulinaemia, which many feel is the key pathogenesis of the syndrome contributes to

hyperandrogenism by direct stimulation of ovarian androgen production, decreasing sex hormone binding globulin and permits the survival of follicles by suppressing apoptosis.⁹ Hyperinsulinaemia generally suggests a lack of receptor sensitivity to insulin effects for unknown reasons.¹⁸ The question remains that what is the prevalence of hyperinsulinaemia in PCOS patients in our part of the world?. Therefore, this study explores this issue.

PATIENTS AND METHODS

This descriptive study included total 64 subjects, which were selected from the gynaecology outpatients department of Isra University Hospital, Hyderabad over a period of two years from January 2002 to December 2003 on the basis of following criteria.

Inclusion criteria:

- Women between 15 – 40 years of age.
- Any one of the following clinical presentation:
 - Secondary amenorrhoea or oligomenorrhoea with weight gain.
 - Secondary amenorrhoea or oligomenorrhoea with infertility.
 - Secondary amenorrhoea or oligomenorrhoea with hyperandrogenism (acne and / or hirsutism).
- Any one of the two evidences of PCOS:
 - a. Ultrasound of the pelvis showing polycystic ovaries (10 or more follicles of 10 mm or less in size).
 - b. LH/ FSH ratio greater than 2:1.

Exclusion criteria:

- Diabetic patient.
- Thyroid disorders.
- Adrenal hyperplasia.
- Hyperprolactinaemia.

Secondary amenorrhoea was defined as cessation of menstruation for six months in reproductive age group and was not due to pregnancy. Oligomenorrhoea means menses at intervals of more than 35 days.¹⁰ Weight gain was a subjective symptom of patients but it was determined by measuring basal metabolic index (BMI). BMI > 25 was considered as over weight while >30 was considered as obese as recommended by The U.S. preventive services task force (USPSTF).¹⁹ Infertility was described as inability of a couple to conceive within one year²⁰ and hirsutism was defined as a woman having increased or excessive body hair particularly on her face, breast or legs compared with the other women of her ethnic group.²¹ All these women underwent detailed history and thorough clinical examination including height in meters and weight in kilograms. They were advised for random blood sugar, serum prolactin and serum TSH to exclude other endocrine disorders. They also underwent serum FSH and LH and ultrasonography of the pelvis to fit into the selection criteria. Ultrasonography was performed to identify small

multiple follicles with necklace appearance on the surface of the ovaries and to exclude other pelvic pathologies. LH/FSH ratio of greater than 2:1¹⁰ was taken in the inclusion criteria. After fulfilling the selection criteria, all these women had their serum insulin levels checked by drawing 2cc of venous blood after a fasting of 12 hours. To standardize the test, it was carried out from single laboratory. Very high and low levels were rechecked. Normal range of values was taken as 3-17 micro U/ml.

RESULTS

Majority of women 37(57.81%) was between 21- 30 years of age (**Table I**). Weight gain was the commonest presenting complain found in 54 women (84.37%) and after calculating the BMI, 29 women (45.31%) were found to be over weight and 17 (26.56%) were obese. Fifty-one women (79.68%) gave history of oligomenorrhoea. Infertility was found in 46 women (71.87%) while signs of hyperandrogenism including hirsutism and acne were seen in 31 (48.43%) and 9(14.06%) women respectively. Ultrasound evidence of PCOS was observed in 39 (60.93%) women and LH/FSH ratio greater than 2:1 was seen in 43 (67.18%) women (**Table II**). Fasting serum insulin levels were normal in 21 (32.18%) women, while 43 (67.18%) women had levels above 17 micro U/ml indicating hyperinsulinaemia (**Table III**).

**TABLE I:
AGE DISTRIBUTION OF THE SUBJECTS (n = 64)**

Age	Number of subjects	Percentage
15 – 20 years	18	28.12
21 – 30 years	37	57.81
31 – 40 years	09	14.07

**TABLE II:
DIAGNOSTIC CRITERIA OF WOMEN WITH PCOS (n = 64)**

Criteria	Number of patients	Percentage
Oligomenorrhoea	51	79.68%
Secondary amenorrhea	13	20.31%
Weight gain	54	84.37%
- Over weight	29	45.31%
- Obese	17	26.56%
Infertility	46	71.87%
Hirsutism	31	48.43%
Acne	09	14.06%
Ultrasound evidence	39	60.93%
LH / FSH ratio > 2:1	43	67.18%

**TABLE III:
SERUM INSULIN LEVELS OF SUBJECTS
DIAGNOSED AS HAVING POLYCYSTIC OVARIAN
SYNDROME (n = 64)**

Insulin level	Number of patients	Percentage
3 – 10 micro U/ml	21	32.81
> 10 – 14 micro U/ml	09	14.06
> 14 – 17 micro U/ml	07	10.93
> 17 micro U/ml	27	42.19

DISCUSSION

PCOS is chiefly a metabolic syndrome which comes to the Gynaecologist.²² It is a subject of continuous studies concerning pathogenesis, diagnostic methods and therapeutic procedures. Now a days, most attention is focused on the role of insulin resistance and hyperinsulinaemia in development of the syndrome.²³ However, one problem remains important and controversial that how many women having PCOS are affected by hyperinsulinaemia. The subjects selected in this study were between 15 – 40 years of age as PCOS is mainly the problem of reproductive age group.²⁴ Most of the patients (57.81%) were between 21 – 30 years of age. Several studies have described that it may be peripubertal in onset and gets worse as the age advances. Although, it is not known at what age they first appear.³ However, Bridges et al (1993) performed 428 ovarian scans in girls aged between three and eighteen years and found polycystic ovaries in 101 (24%). The polycystic ovaries were 6% in 6 years old girls rising to 18% in 10 years and 26% in those aged 15 years. The implication of this study may be that polycystic ovaries are present before puberty and are easier to detect in older girls as the ovaries increase in size.²⁵ Barclay has mentioned that "in PCOS no constellation of findings or set criteria can exclusively be used for a clinical diagnosis or for inclusion in clinical research".⁶ Meanwhile, Khan MI has proposed that presence of menstrual irregularity is must for the diagnosis of PCOS.²⁴ Thus, considering these views as well as NIH 1999 and Rotterdam 2003 definitions of PCOS, the inclusion criteria were decided. All the patients selected in this study had menstrual disturbances followed by oligomenorrhoea (79.68%) and secondary amenorrhoea (20.13%). Amenorrhoea was also the presenting complain for all of the subjects in the series reported by Stein and Leventhal. However, in another study of 1741 women with PCOS, 30% of patients had regular menses, whereas 66% had amenorrhea or oligomenorrhoea.¹

In this study, 54 (84.37%) women gave history of weight gain; 29 (45.31%) over weight and 17

(26.56%) obese on calculating their BMI. The prevalence of over weight and obesity varies between 40 – 70% in different studies.^{3,14,26} Obesity is not a pre-requisite for PCOS but is likely to exacerbate some of its key biochemical features that are important in its pathophysiology. Forty-six women (71.87%) presented with infertility in this study. PCOS has been associated with anovulation in 75% of subjects described by Campbell S.¹⁰ It has also been stated that most women with PCOS ovulate intermittently and may take longer to conceive or may have fewer children than planned. Hyperandrogenism, which is an essential feature in the diagnosis of PCOS was observed in 40 women (62.49%) in the form of hirsutism and acne. Barclay has also stated hirsutism as the best clinical marker of hyperandrogenism.⁶ In two large studies, the prevalence of hirsutism in PCOS varied from 56% in normal weight women to 70% among obese women with PCOS.¹⁷ Ultrasound evidence of PCOS was found in 39 (60.93%) women of our study population. It has been mentioned that diagnosis of PCOS does not always require the presence of polycystic ovaries. However, Khan MI reports that 80 – 100% of women with PCOS have polycystic ovaries.²⁴ LH hypersecretion is a well-established finding in women with PCOS.²⁷ High LH is associated with androgen excess in such women. Raised LH / FSH ratio is found in 45.4% - 94% of women with PCOS.²⁸ While in this study, 43 (67.18%) women had LH / FSH ratio greater than 2:1.

Insulin resistance is defined as a reduced glucose response to a given amount of insulin.² It is known to occur naturally at puberty but to decline again during childhood, it may be that women with PCOS fail to resume levels of insulin sensitivity after puberty.⁸ Multiple etiological factors for this resistance have been suggested. It is also important to note that not all women with insulin resistance develop PCOS. In this study, 27 women (42.19%) had serum insulin levels greater than 17 micro U/ml indicating hyperinsulinaemia, while using the criteria described by Kidson W²⁹ values between 10 – 14 m U/ml indicated mild insulin resistance³⁰ and values above 14 mU/ml indicate moderate or severe insulin resistance. In various studies, insulin resistance has been found in 30 – 70% of patients with PCOS.^{7,10} Using the above values, 43 women (67.18%) in this study had insulin levels greater than 10 mU/ml indicating mild to severe insulin resistance which is similar to the results found in other studies. But, as this was a single centre study with relatively smaller number of women, large multi-centre studies are recommended to establish more conclusive evidence. Moreover, comparison of various studies on PCOS becomes difficult as no fixed criteria have yet been met for establishing its diagnosis.

CONCLUSION

Polycystic ovarian syndrome is the commonest endocrinal disorder found in the women attending gynaecological outpatients department. The fundamental defect of PCOS remains unknown and an area of ongoing study. Hyperinsulinaemia associated with PCOS was found 42.19% in this study, indicating that a significant number of women are having insulin resistance as a prime pathology in polycystic ovarian syndrome increasing the risk of obesity, cardiovascular diseases, diabetes and their complications in the future. But, unfortunately most women are not aware of these risks. Such studies can help us to identify these women at an early age, when preventive measures are most effective.

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