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Article review of

Polycystic Ovarian Syndrome associated with Obesity

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Objectives

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➢ Introduction

PCOS : (the syndrome was first described in 1935 by Stein and Leventhal) Is a syndrome of ovarian dysfunction along with the cardinal features of hyperandrogenism and polycystic ovary morphology[1].

The prevalence of polycystic ovaries seen on ultrasound is around25%of all women but is not always associated with the full syndrome.Clinical manifestations include menstrual irregularities, signs of androgen excess (e.g.hirsutism and acne) and obesity.Elevated serum LH levels, biochemical evidence of hyperandrogenism and raised insulin resistance are also common features[2].

PCOS is associated with an increased risk of type 2 diabetes and cardiovascular events. It affects around 5–10% of women of reproductive age .The etiology of PCOS is not completely clear, although the frequent familial trend points to a genetic cause[1, 2].

➢ What is PCOS?

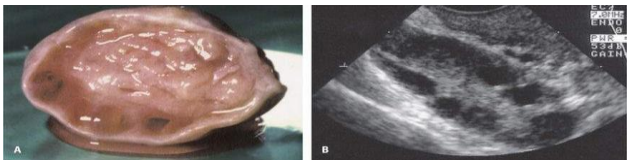
PCOS is the most common hormonal abnormality in reproductive-age women affecting ~7% of this population. The reproductive features of PCOS include increased androgen production and disordered gonadotropin secretion leading to menstrual irregularity, hirsutism, and infertility.[1] In addition to these important reproductive manifestations, PCOS has metabolic characteristics that include prominent defects in insulin action and β-cell function, defects that confer a substantially increased risk for glucose intolerance and type 2 diabetes.[1, 2] Obesity is a common finding in women with PCOS and between 40–80% of women with this condition are reported to be overweight or obese. Familial aggregation of PCOS strongly supports a genetic susceptibility to this disorder.[1]

Furthermore, the metabolic abnormalities associated with PCOS, such as β-cell dysfunction and type 2 diabetes, have heritable components in families of women with PCOS. To date, the genes responsible for PCOS have not been clearly identified. Considering the close association between PCOS and obesity, it is likely that similar or interrelated genes may also predispose to obesity in affected women. No doubt environmental factors (high-caloric diets and reduced exercise) also play a major role in the high prevalence of obesity in women with PCOS.

Until recently, the diagnosis of PCOS was based on the criteria established by a 1990 NIH/National Institutes of Child Health and Human Development (NIH criteria) conference .[12]

➢ Clinical Features

- Oligomenorrhoea/amenorrhoeainupto 75% of patients Pedominantly related to chronic anovulation.
- Hirsutism.
- Subfertility in up to 75% of women.
- Polycystic ovary syndrome (PCOS)



Gross appearance of a polycystic ovary (A) and transvaginal ultrasound scan image (B). .[1, 2]

- Obesity in at least 40% of patients
- Acanthosis nigricans (areas of increased velvety skin pigmentation occur in the axillae and other flexure May be asymptomatic. [2]

➢ Diagnostic Criteria for PCOS

NIH 1990	Rotterdam Criteria*	AE-PCOS society 2006
Diagnosis requires both features:	Diagnosis requires 2 of 3 features:	1.Biochemical and clinical evidence of hyperandrogenism
1. Oligo and/or anovulation	1. Oligo and/or anovulation	2.Dysfunction ovaries
2. Hyperandrogenism Clinical or biochemical	2. Hyperandrogenism Clinical or biochemical	3.Polycystic ovary morphology
3.Long-lasting anovulation	3. Polycystic ovary morphology**	

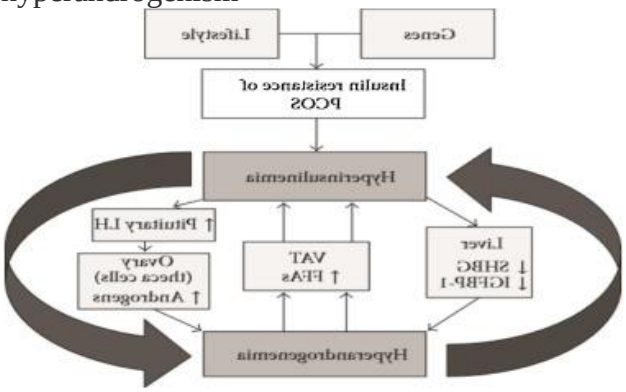
*Other androgen excess or related disorders have to be excluded prior to diagnosis of PCOS.
**Defined by at least one ovary demonstrating an ovarian volume>10 ml or presence of 12 or more follicles measuring 2-9 mm in size. [3]

At the 2003 Rotterdam conference on PCOS, the diagnostic criteria were expanded to include polycystic ovary (PCO) morphology However, this addition to the diagnostic criteria remains controversial because an established minority of women with the biochemical features of the syndrome do not have PCO morphology. [3] Moreover about 25% of asymptomatic women with regular menses have PCO morphology on ultrasound. Many of these women have elevated androgen or luteinizing hormone (LH) levels, but some have normal reproductive function. Furthermore, ovulatory women with PCO and hyperandrogenism may not be as insulin resistant or carry the same increased risk for type 2 diabetes as women diagnosed with PCOS based on the NIH criteria.. Other conditions causing high T were excluded, such as hyperprolactinemia, thyroid diseases, congenital adrenal cortical hyperplasia, Cushing syndrome, androgen secretion tumors, atypical adrenal cortical hyperplasia of 21-hydroxylase deficiency, exogenous androgen administration and so on. The patients were diagnosed with PCOS when they had 2 of the 3 items above and other conditions causing high T were excluded.[3,4]

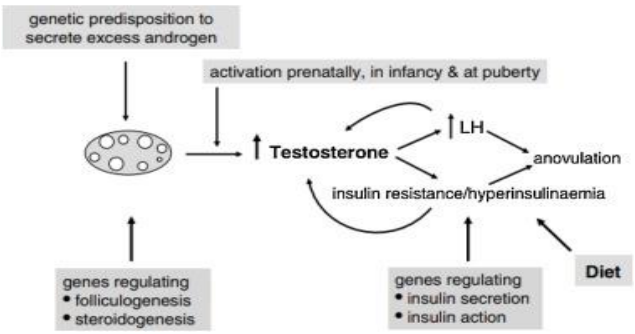
➢ Etiology of PCOS

The genetic and environmental factor is responsible for the etiology of this condition. Unhealthy lifestyle, diet or any infectious mediators increase the risk of PCOS [16]. Due to insulin resistance and its elevated level, the ovaries function disturbs that rises androgen level which leads to anovulation [17]. The level of gonadotrophin-releasing hormone, follicular stimulating hormone (FSH), luteinizing-hormone (LH) and prolactin is also disturbed in case of PCOS [18]. Apart from the environmental factors, there are genetic factors that are responsible for the etiology of PCOS. Its cause involves candidate genes, SNP's. According to databases PCOS etiology involves 241 gene variations [19] Polymorphism or any nucleotide change cause a defect in the transcriptional activity of a gene that leads to PCOS [20] Mostly

genes that encode for the androgen receptor, Luteinizing Hormone receptors, Follicular Stimulating Hormone receptors, Leptin receptors are responsible [21] Gene defect perturbs the biochemical pathway and leads to dysfunction of an ovary. Polymorphism such as StAR polymorphs, FSHR polymorphism, FTO polymorphism, VDR polymorphism, IR and IRS polymorphism, GnRHR polymorphism are found to be involved in PCOS cause [22] PCOS progression and severity increases with the increase in insulin level as well as an androgen. Hyperinsulinemia affects ovarian theca cells and raise androgen level. This condition reduces the hepatic biosynthesis of SHBG and IGFBP-1. Elevated androgen level, on the other hand, stimulates visceral adipose tissue (VAT) that generates free fatty acids (FFA's) which contributes in insulin resistance [23] Genetic predisposition with PCOS, a pathway describes hyperandrogenism

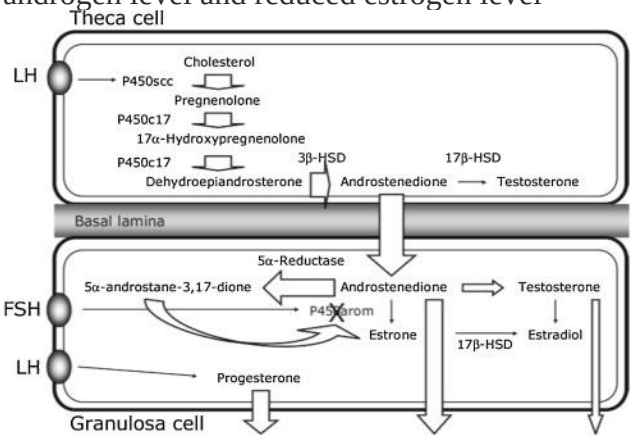


how insulin resistance effects the ovarian theca cells and perturbs its functioning [24]



. A defect in the pituitary axis elates testosterone and LH. It also leads to insulin resistance. Together insulin resistance and high level of androgen subsidize in the pathway of anovulation [25]

depicts a pathway that describes how steroidogenesis enzyme affect the theca cells of an ovary. 5ά-reductase activity increased that elevates 5ά-androstane -3, 17 Dione concentrations and inhibit the activity of aromatase in the granulosa cells. In the case of PCOS, LH and progesterone are expressed in the granulosa cells which results in high androgen level and reduced estrogen level [24]



effect of steroidogenesis enzyme and theca cells of an ovary.

➢ Management

Management of PCOS involves the following:

• Physical activity. The benefits of physical activity for the populace are legion and include interesting cross talk between muscle and brain.[25] As in obesity management in general, maintenance of physical activity and exercise forms a key aspect of lifestyle advice for women with PCOS.[26] Benefits include promotion of weight-loss; fasting insulin levels and waist circumference; free androgen index; and blood pressure, lipid profile, glucose levels, and reduction in fat mass. It is important to consider whether PCOS may contribute towards weight-

gain and obesity (or at least resistance to effective weight-loss), [26] through effects of the condition on ability to engage in physical activity, mediated by possible PCOS-related emotional and physical factors. [27] It is important to highlight that the factors discussed below may also apply to the general obese populace regardless of PCOS status, given the complex association between obesity and emotional and physical functioning. [28]

• Combined oral contraceptive pill (COCP) to regulate menstruation. This also increases sex hormone-binding globulin, which will help reduce androgenic symptoms.

• Cyclical oral progesterone: used to regulate a withdrawal bleed.

• Clomiphene :this can be used to induce ovulation where subfertility is a factor.

• Lifestyle advice: dietary modification and exercise is appropriate in these patients as they are at an increased risk of developing diabetes and cardiovascular disease later in life.

• Aerobic exercise has been shown to improve insulin resistance.

• Weight reduction.

• Ovarian drilling, a laparoscopic procedure to destroy some of the ovarian stroma that may promptovulatory cycles [28],[29]

• Treatment of hirsutism/androgenic symptoms:

Eflornithine cream (Vaniqua) applied topically; cyproterone acetate (an antiandrogen contained in the Dianette contraceptive pill, sometimes usedalone) metformin: this is beneficial in a subset of patients with PCOS, those with hyperinsulinaemia and cardiovascular risk factors. It improves parameters of insulin resistance ,hyperandrogenaemia and ovulation and acne in PCOS, and may aid weight loss.It is less effective than clomiphene for ovulation induction and does not improve pregnancy outcome. [28]

GnRH analogues with low- dose HRT: this regime should be reserved for women intolerant of othertherapies Surgical treatments (e.g. laser or electrolysis) [30],[31]

➢ Insulin Action in PCOS: Relation with Obesity

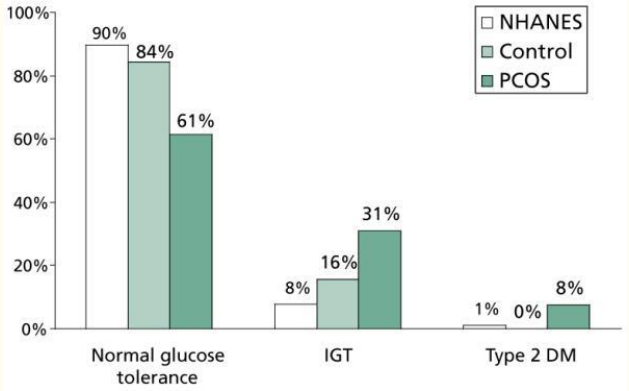
Insulin resistance is a common finding in PCOS that is independent of obesity. Insulin-mediated glucose disposal, reflecting mainly insulin action on skeletal muscle is decreased by 35–40% in women with PCOS compared to weight comparable reproductively normal women.[2] This defect is independent of but substantially worsened by obesity. In contrast, hepatic insulin resistance, characterized by both increased postabsorptive glucose production and reduced sensitivity to insulin mediated suppression of endogenous glucose production, is present only in obese women with PCOS compared to control women of comparable body weight.[2] This synergistic deleterious effect of obesity and PCOS on endogenous glucose production may be an important factor in the pathogenesis of glucose intolerance.[2]

Fasting insulin levels are increased in PCOS. Nonetheless, there are defects in insulin secretion that are independent of obesity.[2] These abnormalities are more pronounced in women with PCOS who have a first-degree relative with type 2 diabetes. In PCOS, basal insulin secretion is increased, but insulin responses to glucose are inappropriately low.[2] Under normal circumstances, the relation between insulin secretion and sensitivity is constant so that changes in insulin sensitivity are accompanied by reciprocal changes in insulin secretion that maintain normal glucose tolerance; this relationship is known as the "disposition index." Both obese and nonobese women with PCOS have lower a disposition index compared to weight-matched reproductively normal women.[2] Furthermore, disposition index is significantly lowered by PCOS as well as obesity. In summary, PCOS is associated with

defects in insulin sensitivity and secretion that are further exacerbated by obesity.

➢ Glucose Tolerance in PCOS: Relation with Obesity

Considering the baseline defects in insulin sensitivity and secretion in PCOS and the deleterious impact of obesity on these measures, women with this condition are expected to have a high prevalence of impaired glucose tolerance (IGT, defined by a 2h post-challenge glucose level 140–200 mg/dl) and type 2 diabetes. A number of studies have confirmed a high prevalence of these abnormalities in obese reproductive-age women with PCOS. In a study of 254 reproductive-age women with PCOS and 80 control women of comparable ethnicity, age, and weight.[2,4] the prevalence of glucose intolerance in women with PCOS (~40% combined IGT and type 2 diabetes) was much higher than that reported in the control women from the same study (14% with IGT and 0% with type 2 diabetes) as well as that reported in a major population-based study. Furthermore, the risk for developing glucose intolerance increased with increasing body mass index (BMI); the prevalence of IGT and type 2 diabetes were much lower in nonobese women with PCOS (10.3% and 1.5%, respectively) compared to the obese and the overall population. The study also revealed that normal fasting glucose levels in women with PCOS does not exclude glucose intolerance in these women. Of women diagnosed with type 2 diabetes, 58% had normal fasting glucose levels and were identified based on elevated 2h glucose levels by an oral glucose tolerance test.



Women with PCOS (black bars) had much higher prevalence of abnormal glucose tolerance compared to control women of similar ethnicity, age, and weight (gray bars) (P=0.02) as well as compared to reproductive-age women from the Second National Health and Nutrition Examination Survey (NHANES) (white bars). [4]

In another study of women with PCOS,[5] the overall prevalence of glucose intolerance was 45% (35% with IGT and 10% with type 2 diabetes). Women with PCOS and type 2 diabetes were significantly more obese than their counterparts with normal glucose tolerance. Moreover, repeat determination of glucose tolerance after 2.5 years revealed an accelerated rate of conversion from IGT to type 2 diabetes that was strongly dependent upon BMI. Similarly in this study, the fasting glucose levels did not reliably predict the 2h glucose levels after a glucose tolerance test. Studies from Australia have also revealed a high prevalence of abnormal glucose tolerance in women with PCOS in association with obesity;[6] obese women (BMI≥30 kg/m^2) had a 10-fold increase and over-weight women (BMI 25–30 kg/m^2) had a 7-fold increase in the risk of abnormal glucose tolerance compared with normal weight (BMI<25 kg/m^2) women with PCOS. [4,5,6]

In summary, PCOS is associated with high rates of glucose intolerance resulting from defects in insulin action and β-cell function. Obesity substantially exacerbates these defects so obese reproductive-age women with PCOS are at very

high rates of glucose intolerance. Detection of glucose abnormalities in women with PCOS is best performed by means of glucose tolerance testing, since fasting glucose levels may be normal despite presence of glucose intolerance.

➢ Can Obesity Cause PCOS?

Reproductive disturbances are more common in obese women regardless of the diagnosis of PCOS. Obese women are more likely to have menstrual irregularity and anvolatory infertility than normal-weight women. In reproductive-age women, the relative risk of anovulatory infertility increases at a BMI of 24 kg/m^2 and continues to rise with increasing BMI.[7] Consistent with a pathophysiologic role for obesity, weight reduction can restore regular menstrual cycles in these women. [7]

Despite the higher frequency of reproductive abnormalities in obese women, the majority of obese women do not develop hyperandrogenemia and do not have PCOS. In obesity increased androgen production has been reported especially in women with upper-body obesity. However, androgen clearance rates are also increased, and circulating bioavailable androgens remain in the normal range. In contrast, in PCOS bioavailable androgen levels are increased.[8] This abnormality is further worsened by obesity, especially central obesity, since sex hormone binding globulin, or SHBG, levels are reduced in this state due to hyperinsulinemia. Furthermore, PCOS is characterized by abnormalities in the gonadotropin hormone releasing hormone, or GnRH, pulse generator leading to preferential increase in LH release over follicle stimulating hormone (FSH).[8] These abnormalities are independent of obesity. Moreover, obese reproductively normal women do not have abnormalities in 24-hour LH and FSH plasma concentrations.

Nonetheless, the prevalence of PCOS among obese reproductive-age women has not been well studied. In a recent study from Spain, PCOS was 5-fold more common among unselected premenopausal overweight or obese women seeking advice for weight loss compared to that of the general population (28.3% vs 5.5%, respectively).[8] In this study, the increased prevalence of PCOS in overweight and obese women was irrespective of the degree of obesity and was independent of the presence or absence of the metabolic syndrome or its features.[8] The study demonstrates the prevalence of PCOS may be markedly increased in overweight and obese women. Routine screening by obtaining at least a menstrual history and a careful evaluation for hyperandrogenism may be indicated in these women as well. [7,8]

➢ Does PCOS Cause Obesity?

Androgens play an important role in determination of body composition. Men have less body fat with greater distribution of fat in the upper portion of the body (android) compared to women, who tend to accumulate fat in the lower portion of the body (gynoid). Vague first reported that the prevalence of diabetes, hypertension, and atherosclerosis was higher in women with android obesity compared to gynoid obesity.[9] Moreover, he observed that the prevalence of android body habitus increases in women after the age of menopause and women with android obesity tend to have features of hyperandrogenism such as hirsutism.[9] Women with upper-body obesity have also been noted to have decreased insulin sensitivity and are at higher risk for cardiovascular disease and diabetes. Independent of BMI, women with PCOS have been reported to have a high prevalence of upper-body obesity as demonstrated by increased waist circumference and waist-hip ratio compared to BMI-matched control women. Consistent with these findings, studies using dual-energy X-ray absorptiometry have revealed increased accumulation of central fat in women with PCOS.[10]

Chronic exposure to higher testosterone levels in women with PCOS may modify body fat

distribution in these women. Support for this hypothesis is provided by studies of androgen administration in nonobese female to male transsexuals that lead to increases in visceral fat and adversely impact insulin sensitivity.[11] In post-menopausal women exposure to androgens increases visceral fat in both obese and normal-weight women.[12] In rats, testosterone administration of a single high dose early in life leads to development of insulin resistance and centralization of adipose tissue mass as an adult.[13] It may be that early androgen exposure adversely impacts future body fat distribution with greater accumulation of central fat.

However, few studies have examined visceral fat content in women with PCOS. Studies of isolated abdominal fat cells from women with PCOS have revealed larger-sized cells in both obese and nonobese women with PCOS compared to control women, suggesting a preferential abdominal accumulation of adipose tissue.[14] Femoral adipocytes are smaller in obese women with PCOS than reproductively normal women consistent with a shift to android body fat distribution in PCOS women. These observations raise the hypothesis that hyperandrogenemia may contribute to the development of visceral adiposity in PCOS women necessitating further investigation in this area.

➢ Hormonal Regulations of Weight and Appetite

Lower fasting levels of the peptide hormone, ghrelin, have been reported in women with PCOS compared to weight-matched control women. Ghrelin is produced by the gastric endocrine cells and has been implicated in regulation of appetite and body weight. [15] Ghrelin levels increase sharply before meals leading to hunger and initiation of food intake and drop after feeding leading to suppression of appetite and satiety. Fasting ghrelin levels are reported to be lower in obese individuals due to chronic positive energy balance. However, there is evidence that ghrelin homeostasis in PCOS may be dysregulated. In addition to lower fasting ghrelin levels, women with PCOS have less marked post-parandial reduction in the level of this hormone, as well as less satiety following a test meal. Lack of suppression of ghrelin following food intake may interfere with meal termination and lead to weight gain in these women.[15]

➢ Conclusions

Obesity is a common finding in PCOS and aggravates many of its reproductive and metabolic features. The relationship between PCOS and obesity is complex, not well understood, and most likely involves interaction of genetic and environmental factors.

➢ Summery

Overall, these data indicate that obesity only modestly increases the risk of PCOS, if at all, and that the prevalence of obesity in PCOS most strongly reflects environmental factors. In this study we have not assessed the potential contribution of any specific environmental factor. However, it is likely that changes in the quantity, type, and quality of dietary intake and in the degree and type of physical activity over time may have had significant influence on the prevalence of obesity among PCOS women, as they have in the general population [32]. Finally and notwithstanding our observation that the role of obesity in altering the development or prevalence of PCOS appears to be modest, it is also clear that the concomitant presence of obesity will worsen the phenotypic and metabolic presentation of the disorder [33] and that weight loss and lifestyle management offers a beneficial effect on the ovulatory and metabolic dysfunction of obese women with PCOS [34].

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