JPMA (Journal Of Pakistan Medical Association) Vol 53 ,No.21,Jan. 2008
Review Article

Polycystic Ovarian Syndrome: a new perspective

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Introduction

Polycystic ovarian syndrome (PCOS) is sometimes called Stein-Leventhal Syndrome after the two doctors who first described it in 1935.1 It is the most common ovarian disorder with typical features of obesity, anovulation, hyperandrogenism, hirsutism and infertility. The accepted nomenclature for the syndrome is PCOS, despite the fact that polycystic ovaries are non-specific findings and can occur in women with regular cycles and no hormonal derangements.2 Other names such as hyperandrogenic chronic anovulation and functional ovarian hyperandrogenism have failed to gain wide acceptance.

Its occurrence varies from 1-8% in general population depending upon the diagnostic criteria, as there is no universal definition for this syndrome.3-5 Despite extensive research, the etiology and the mechanisms underlying PCOS are largely unknown, but there is considerable evidence suggesting that insulin plays the basic pathologic role along with a genetic component to the syndrome.

It is not purely an ovarian disease but an extremely heterogeneous clinical syndrome that should be recognized as a systemic endocrine and metabolic disorder. The first insight into the biochemical derangements came in the mid 1950s with the detection of elevated urinary luteinizing hormome (LH) levels; later increased androgen production was documented. Abnormalities in the hypothalamic-pituitary-ovarian axis with increased pulsatile LH release and increased pituitary gonadotroph sensitivity to gonadotropin releasing hormone were characterized in the early 1970s. In mid 1980s it was found that insulin resistance and hyperinsulinemia are also important components of PCOS that play a causal role in both hyperandrogenemia and chronic anovulation.6,7

These metabolic derangements may predispose women with PCOS to a range of diseases such as type 2 diabetes mellitus, dyslipidemia, endometrial cancer and coronary artery syndrome.

Prevalence

Data on the prevalence of PCOS is variable mainly due to the different sets of criteria for diagnosis. Studies in which polycystic ovaries were detected using ultrasonography report a prevalence of 21-22%, which does not give us an accurate estimate as many

women with polycystic ovaries are endocrinologically normal.2,8,9 Data from a cross-sectional study in Greece indicate 9% prevalence while defining PCOS as having oligomenorrhoea and hyperandrogenism.10 Another study by Knochenhauer and coworkers11 assessed menstrual cycle characteristics and clinical androgen excess among 277 women undergoing a routine pre-employment history and physical examination in Alabama. The estimated prevalence was 4.6% with a possible range of 3.5-11.2%.

Spectrum of Clinical Presentation

1. Menstrual Dysfunction

Irregular and unpredictable uterine bleeding is the hallmark of PCOS, 85-90% women have oligomenorrhoea while 30-40% present with amennorhoea. These symptoms are clinical features of anovulation, but not all patients have anovulatory cycles as corpus luteum formation at the time of surgery has been found in approximately 16% of women with PCOS.11

2. Androgen Excess

Approximately 80% of PCOS patients have excessive hair growth that usually has a male pattern.12 Prolonged exposure to high levels of circulating androgens may even cause temporal balding. Acne is commonly seen but severe form of androgen excess such as clitoromegaly is absent.

3. Infertility

Infertility forms a part of the presenting complaint of significant number of patients.12 Anovulation is thought to be the primary defect responsible.

4. Obesity

The onset of obesity has been correlated with the appearance of menstrual dysfunction. Patients usually have an android pattern of obesity.13

Predisposing Factors

Studies have revealed that obesity is a predisposing factor for PCOS, weight reduction may cause improvement in menstrual irregularities.14-16 Ethnicity may determine the risk for PCOS, women with certain racial background show increased incidence of the syndrome.17 A study conducted in the U.S., France, Italy and Japan revealed that PCOS might manifest differently in different populations even when the biochemical androgen excess and insulin tolerance test values are comparable.18 Available studies suggest that there is also a strong familial component to PCOS regardless of the diagnostic criteria used to ascertain probands and to assign affected status in kindreds.

Pathogenesis

Chronic anovulation along with hyperandrogenemia results in an increased number of atretic follicles (which become cysts) and increased interstitial tissue in the stroma of the ovaries19,20 thus giving us the typical picture of the ovaries in PCOS.

Plasma androgen is produced directly by secretion and indirectly by peripheral metabolism of secreted precursors. Both the ovaries and the adrenals in response to their trophic hormones LH and adrenocorticotropic hormone (ACTH), secrete these androgens

and their precursors. Androgens in women are not specifically under negative feedback control by these pituitary hormones because they are by-products of estradiol and cortisol secretion. The rate-limiting step in steroidogenesis is the formation of pregnenolone from cholesterol, which is regulated by trophic hormones. The rate-limiting step in androgen formation is regulation of cytochrome P450c17, a bifunctional enzyme with both 17,20-lyase and 17-hydroxylase activities. Cytochrome P450c17 converts progesterone to 17a-hydroxyprogesterone via its 17a-hydroxylase activity, and then converts 17a-hydroxyprogesterone to androstenedione by virtue of its 17,20-lyase activity in the ovarian theca cells. The expression of cytochrome P450c17 is dependant on the concentration of trophic hormones, LH in the ovary21-23 and ACTH in the adrenal cortex.24,25 Thus, dysregulation of the cytochrome P450c17 gene may result in functional ovarian hyperandrogenism alone, functional adrenal hyperandrogenism alone, or both together. Other subtle generalized disturbances of steroid metabolism, including tendencies toward excessive estrogen and cortisol secretion is frequently present. The exact cause of dysregulation of steroidogenesis is unknown.

Ovarian Dysfunction

Functional ovarian hyperandrogenism is found in 70% of the patients with PCOS.26 The presence of enlarged polycystic ovaries suggests that the ovaries are the primary sites of abnormality in PCOS. Theca cells from polycystic ovaries secrete abnormal amounts of steroids in culture both before and after LH stimulation.27 But we know that LH has a stimulatory effect on theca cells, hence other factors also come into play. However, when patients with PCOS are given LH analogue human chorionic gonadotropin (HCG), they show 17-hydroxyprogesterone and androstenedione hyper-responsiveness.28,29 Recent evidence suggests that insulin is capable of acting through its own receptor in polycystic ovaries and causes theca cell proliferation.30,31 Studies reveal that cytochrome P450c17 activity is increased due to stimulation by insulin.32,33 Insulin also stimulates ovarian androgen production34-38, lowers serum sex-hormone binding globulin (SSBG)39,40 and also enhances endogenous and exogenously induced release of LH mediated by gonadotropin releasing hormone (GnRH). Insulin like growth factors (IGFs) may also contribute to the theca cell proliferation of polycystic ovaries.41

Adrenal Dysfunction

Functional adrenal hyperandrogenism, glucocorticoid-suppressible ACTH-dependant 17-ketosteroid excess is found in approximately one half of hyperandrogenic women and patients with functional ovarian hyperandrogenism.26 There is evidence suggesting that patients with PCOS sometimes have mild increases in plasma ACTH and cortisol responsiveness to corticotropin-releasing hormone, spontaneous ACTH and cortisol secretions42, cortisol responsiveness to ACTH and urinary free cortisol excretion.43

Peripheral Steroid Metabolism

Peripheral steroid metabolism is altered in PCOS. Rodin and co-workers reported evidence supporting the dysregulation of 11b-hydroxy steroid dehydrogenase in PCOS.44 Marginally increased activity of 5a-reductase has also been reported44,45 which may attribute to androgen excess.46 Adipose tissue converts inactive precursors to testosterone and estrone47 and has an important role in the pathophysiology. In some

cases of chronic hyperandrogenic anovulation, weight reduction normalizes androgen levels48-52, this may also be due to the lowered insulin levels.29,54

Insulin Resistance

In 1980, it was first reported that patients with PCOS had high insulin levels suggesting that they were insulin resistant.54 It was also observed that such patients had subtle acanthosis nigricans, which was a cutaneous marker for insulin resistance.55 Studies have confirmed that insulin resistance is limited to women with polycystic ovary morphology and chronic anovulation.56 Insulin-sensitizing drugs have restored ovulation in PCOS57,58 proving that insulin-resistance is a unique feature of the syndrome of chronic anovulation and hyperandrogenemia.

A recent study by Legro and colleagues revealed that approximately 40% of women with PCOS had glucose intolerance, 31% had impaired glucose tolerance and 7.5% had Type 2 diabetes mellitus59, these rates were significantly higher than those of the controls.

In the presence of peripheral insulin resistance, pancreatic b-cells insulin secretion increases in a compensatory fashion and type 2 diabetes mellitus develops when the compensation is no longer sufficient to maintain euglycemia.60 Now there is evidence suggesting that ß-cell dysfunction is, in addition to insulin resistance, a feature of PCOS.61-63 It has been suggested that protein kinase C-mediated serine phosphorylation of the insulin receptor is important in the pathogenesis of hyperglycemia-induced insulin resistance.64

Cause of high insulin in PCOS

Hyperinsulinemia is probably the result of both increased insulin secretion and decrease in insulin clearance. A study in women with PCOS found decreased hepatic insulin extraction.63 Molar ratios of circulating insulin to C-peptide are increased in PCOS, suggesting decreased hepatic extraction of insulin, but such ratios also reflect insulin secretion.65

Effect of Androgens on Insulin Resistance

Androgens produce mild insulin resistance. Prolonged testosterone administration to female-to-male transexuals to produce circulating testosterone levels in the normal male range resulted in modest but significant decreases in insulin-medicated glucose uptake in euglycemic clamp studies.66 Modest improvements in insulin sensitivity in PCOS during androgen suppression or anti-androgen therapy have been found when less insulin-resistant, less obese or non-obese women with PCOS have been studied.67,68 However suppressing androgen level does not completely restore insulin sensitivity to normal and administering androgens does not produce insulin-resistance of the same magnitude as that seen in PCOS.

Diagnosis and Evaluation

Setting the diagnostic criteria for PCOS is a challenge for practitioners since there is no one universal definition for the syndrome. As researchers unveil new pathophysiologic mechanisms underlying the manifestations of PCOS, the diagnostic criteria are correspondingly modified. The consensus towards a definition was reached in 1992.69 The diagnosis is based mainly on clinical history and physical examination. Though

laboratory examinations may be performed, they are mainly for excluding disorders of hormone production, enzyme deficiencies and other metabolic disorders.

Differential Diagnosis

As PCOS has a very wide clinical spectrum resulting from hyperandrogenemia and anovulation it becomes necessary to exclude conditions with similar presentations. These include functional and neoplastic processes. More detail about differentiating these conditions from PCOS is described in the following table:

Symptomatology

Though the clinical presentation of PCOS may resemble several other disorders, they most frequently occur in PCOS. Identification of the following three features is important when diagnosing PCOS. However, it must be kept in mind that these symptoms may not be present in all the patients.

1. Development of hirsutism.
2. Episodes of irregular menstrual bleeding.
3. The gradual onset of symptoms.

The development of hirsutism in PCOS is gradual and must be distinguished from that due to an androgen-producing neoplasm. Patients with PCOS usually have irregular menses and most of them have less than 6 episodes a year. The most striking feature in these patients is the lack of the premenstrual symptoms. Thus the episodes are unpredictable and anovulation is suggestive along with a history of failure to conceive. Symptoms are mostly recognized at the time or soon after puberty. These include hirsutism, obesity and irregular bleeding. Though a regular bleeding pattern is usually attained by one and a half years after menarche, if this period exceeds three years, PCOS must be suspected.

Physical Examination

The original description of PCOS can be applied to most patients; these features may vary considerably in different ethnic settings, as it is now believed that they may have a possible genetic link. The following factors should be assessed in the physical examination.

1. Obesity
2. Signs and symptoms of hyperandrogenism
3. Acanthosis nigricans
4. Ovaries

Bilaterally enlarged ovaries are found in PCOS on pelvic examination, which may be facilitated by ultrasound imaging. In most cases of PCOS, hyperandrogenism is manifested only as hirsutism. Some degree of temporal balding and acne formation is usually seen, however extreme expressions of androgen excess such as virilization and clitoromegaly are not typical findings. Fifty percent of the patients with PCOS are obese.70 This obesity is characterized by an increased waist-to-hip ratio or an android appearance as opposed to truncal obesity.13 It is important to distinguish this obesity from that of Cushing's syndrome or that due to excess cortisol production in patients who

are massively overweight. Despite their obesity patients with PCOS do not display moon facies or abdominal striae. Acanthosis nigricans is usually seen in obese patients with PCOS at the nape of the neck, the axilla, the area beneath the breasts and other intertrigenous areas.

Investigations

Laboratory tests performed while suspecting PCOS are usually done for exclusion of other disorders. Clinical suspicion of PCOS warrants patients to undergo a minimum endocrinological evaluation. If the patients exhibit mild to severe hirsutism associated with rapid onset of symptoms, assays for serum total testosterone and dehydroepiandrosterone sulfate (DHEA sulfate) should be done to exclude the possibility of an androgen-producing tumor of the ovary and the adrenal glands respectively. Levels of 17-hydroxyprogesterone may be determined to detect congenital adrenal hyperplasia (CAH) owing to 21-hydroxylase deficiency. A circulating level greater than 3ng/mL warrants further evaluation by an ACTH stimulation test.

Though LH levels are increased and so is the LH to follicle stimulating hormone (FSH) ratio in PCOS, determination of the circulating levels of these glycoproteins has not proven to be useful as a diagnostic tool. Similarly, levels of circulating serum testosterone are increased but not used for diagnosis; however, such an assay may be a part of the initial screening hormone panel for PCOS and a utility to determine the efficacy of treatment of hirsutism.71

Long Term Disease Risks

The role of insulin in the pathogenesis of PCOS is far more than what health practitioners ever believed. Almost 15% of the patients with PCOS are diabetic. The high insulin levels cause a disbalance between the androgen and estrogen ratio with higher levels of circulating androgens, which reduces the protective effect of estrogens on the cardiovascular system. Dyslipidemias occur with relatively high levels of total cholesterol, low density lipoproteins (LDL) and triglycerides, and lower levels of high density lipoproteins (HDL)72, predisposing to faster atherosclerosis and putting the patient at a greater risk for hypercholestrolemia and cardiovascular diseases.73 Studies reveal that the risk for coronary heart disease is elevated threefold in women having type II diabetes mellitus74 and twofold in women with hypertension.73 Obesity75 and increased waist-to-hip ratio76 are also risk factors for cardiovascular disease in women. All these risk factors are usually present in patients with PCOS and the calculated risk for myocardial infarction in such women is seven times more than that in a normal healthy woman.77

Treatment

Women with PCOS have both abnormally elevated LH secretion78,79 and hyperinsulinemia as a result of insulin resistance.80 The combination of hypersecretion of LH and insulin causes ovarian androgen overproduction.81 In turn, ovarian androgen overproduction causes hirsutism and prevents normal ovarian follicle growth, preventing regular ovulation. Lowering LH hypersecretion (oral contraceptive pills or GnRH agonist analogues) can treat PCOS or by reversing the hyperinsulinemia that is caused by insulin resistance (weight loss or metformin). An intriguing idea is to use oral contraceptives

plus metformin in combination to simultaneously attack the 2 principle causes of PCOS: hypersecretion of LH and insulin.

In one recently reported clinical trial, Elter and colleagues82 randomized 40 non-obese women with PCOS to treatment with either an oral contraceptive alone (ethinyl estradiol 35 micrograms daily plus cyproterone acetate 2 mg daily) or the oral contraceptive plus metformin 500 mg 3 times daily for 4 months. In both groups, circulating androgens, such as androstenedione and testosterone, were significantly suppressed from baseline by 4 months of treatment. However, androstenedione levels were more suppressed by the combination therapy of the oral contraceptive plus metformin than by the oral contraceptive alone. In addition, weight loss occurred in the combination therapy group, but weight loss did not occur in the group treated with the oral contraceptive alone. An objective measure of hirsutism, the Ferriman-Gallwey score, was similarly improved in both treatment groups. This study suggests that the combination of metformin plus an oral contraceptive may be especially useful when an important objective of treatment is weight loss. For the treatment of hirsutism, at least over 4 months, the oral contraceptive performed as well as the combination of metformin plus the oral contraceptive.

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