INTRODUCTION
Polycystic Ovarian Syndrome (PCOS) is the most common cause of hyperandrogenism in women and adolescent girls. The signs and symptoms may vary widely between as well as within individuals over time. Although symptoms of androgen excess may vary between ethnicity, PCOS appears to equally affect all races and nationalities. It affects 4 to 12 percent of reproductive-age women. The incidence in Indian population has been estimated to be between 4 and 11% among women in reproductive age group. According to European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) Consensus, affected individuals must have two out of the three following criteria: (1) oligo- and/or anovulation, (2) hyperandrogenism (clinical and/or biochemical), and (3) polycystic ovaries on sonography evaluation. Other etiologies may also lead to oligo-ovulation and/or androgen excess such as congenital adrenal hyperplasia, androgen secreting tumor and hyperprolactinemia.

ETIOLOGY
Several genes may play a role in PCOS pathogenesis, among others are CYP11a gene and insulin receptor gene on chromosome 19p13.2. CYP11a gene, found in human ovarian theca cells, encodes the cholesterol side-chain cleavage enzyme, the enzyme that performs the rate-limiting step in steroid biosynthesis. Some have suggested an autosomal dominant inheritance, first-degree male relatives of women with PCOS have been shown to have significantly higher circulating dehydroepiandrosterone sulfate (DHEAS) levels than control males.

PATHOPHYSIOLOGY
Alterations in gonadotropin-releasing hormone (GnRH) pulsatility lead to preferential production of luteinizing hormone (LH) compared with follicle-stimulating hormone (FSH). LH stimulates ovarian androgen production, while the relative paucity of FSH prevents adequate stimulation of aromatase activity within the granulosa cells, thereby decreasing androgen conversion to the potent estrogen estradiol. Increased intrafollicular androgen levels result in follicular atresia. Lack of follicular development results in anovulation and subsequent oligo-amenorrhea.

Elevated serum androgens (primarily androstenedione) are converted in the periphery to estrogens (primarily estrone). As conversion occurs primarily in the stromal cells of adipose tissue, estrogen production will be augmented in obese PCOS patients. This conversion results in chronic feedback at the hypothalamus and pituitary gland, in contrast to the normal fluctuations in feedback observed in the presence of a growing follicle and rapidly changing levels of estradiol.

ABSTRACT
Polycystic Ovarian Syndrome (PCOS) is one of the most common endocrinopathies, affecting 5-10% of women of reproductive age. Diagnosis is based on European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine Consensus. A complete understanding of PCOS pathophysiology is still elusive. The heterogeneity of the syndrome reinforces its multifactorial nature, and pinpointing the etiologic factor is not yet possible; treatment focuses on clinical improvement based on the goals of patient and clinician. The use of insulin-sensitizing medications such as metformin recently has become an area of great interest. Its use may reduce the risk of hyperinsulinism, type 2 diabetes, and metabolic syndrome.

Key words: Gene, metformin, polycystic ovarian syndrome, treatment

ABSTRAK

Kata kunci: Gen, metformin, sindrom polikistik ovarium, pengobatan

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Unopposed estrogen stimulation of the endometrium may lead to endometrial hyperplasia. Increased insulin resistance has been associated with several disorders including type 2 diabetes mellitus, hypertension, dyslipidemia, and cardiovascular disease. Insulin resistance due to genetic abnormalities and/or increased adipose tissue contributes to follicular atresia in the ovaries as well as the development of acanthosis nigricans in the skin. Insulin stimulate synthesis and secretion of VLDL in the liver resulting in hypertriglyceridemia, which in turn enhances post-prandial accumulation of lipoproteins (LDL, VLDL) in plasma with lowering of HDL cholesterol.

Women with PCOS display decreased sex hormone-binding globulin (SHBG) levels. This glycoprotein, produced in the liver, binds most sex steroids. Because of suppressed SHBG production, less circulating androgen is bound and thus more remains available to bind with end-organ receptors. It caused some women with PCOS will have total testosterone levels in the normal range, but will be clinically hyperandrogenic due to elevated free testosterone levels. The unbound circulating estrogen may cause higher endometrial cancer risk in PCOS patient.

In some hair-bearing areas, androgens stimulate sebaceous glands, and increased sebum may lead to acne. In other areas, vellus follicles respond to androgens and are converted to terminal follicles, leading to hirsutism. Under the influence of androgens, terminal hairs that were not previously dependent on androgens revert to a vellus form and balding results.

Women with PCOS are considered to be at increased risk of miscarriage after either spontaneous or assisted conception. Rates of early pregnancy loss are reported to be three times higher than those in normal women (30-50% in PCOS vs 10-15% in normal women).

The finding of high prorenin concentrations in immature and atretic human follicles, compared to mature ones, suggest a possible role of renin in ovarian dysfunction. Interestingly, in the ovarian tissues from PCOS subjects, the increased immunohistochemical staining of renin, localized in both granulosa and theca cells, suggest a role of renin in PCOS.

Binding of renin/prorenin to its common receptor leads to increased renin activity, increased plasminogen activator inhibitor-1 production and induces cellular hypertrophy and vascular fibrosis. These findings suggest that hyperreninemic state plays an important role in the development of end-organ damage.

**SIGNS AND SYMPTOMS**

1. Menstrual dysfunction, ranging from amenorrhea to oligomenorrhea to episodic menometrorrhagia with anemia.
2. Hyperandrogenism: increased muscle mass, androgenic alopecia, deepening of voice, and clitoromegaly.
3. Hirsutism. Hirsutism should be distinguished from hypertrichosis, which is a generalized increase in lanugo, that is, the soft, lightly pigmented hair associated with some medications and malignancies.
4. Acne.
5. Insulin resistance: Impaired Glucose Tolerance Test and Type 2 Diabetes Mellitus.
6. Acanthosis nigricans.
7. Dyslipidemia.
8. Infertility.

**Long term consequences**

During the last decade, research has revealed an association of PCOS with hyperinsulinemia, insulin resistance and the metabolic syndrome, which could possibly result in increased morbidity due to type 2 diabetes mellitus (DM) and cardiovascular disease (CVD). Women with PCOS and hyperinsulinemia have low-grade chronic inflammation reflected in an elevation of C-Reactive Protein and endothelial dysfunction, which has recently been linked to the development of atherosclerosis and the formation of atheromatous plaques.
Recently, it has also been shown that hyperandrogenemia in PCOS women seems to be an independent risk factor for the development of hypertension (HT). An increased prevalence of endometrial hyperplasia in PCOS subjects eventually resulting in carcinoma has been reported for many years, but the actual risk seems unclear. Endometrial biopsy is recommended in women who have an Endometrial Hyperplasia.

If pregnancy occurs, the presence of insulin resistance and hyperinsulinemia are responsible for a higher rate of obstetrics complications such as gestational DM, early pregnancy loss, hypertension in pregnancy and preterm birth.

DIAGNOSIS
Polycystic ovarian syndrome is often referred to as a diagnosis of exclusion. Thus, routine exclusion of other potentially serious disorders that may clinically appear like PCOS is warranted. If the patient comes with signs and symptoms of oligo- or anovulation, then hyperthyroidism, hypothyroidism, hyperprolactinemia, hypo gonadotropic hypogonadism, and premature ovarian failure must be excluded. If the patient comes with hirsutism, then late-onset congenital adrenal hyperplasia, androgen-secreting ovarian tumor, androgen-secreting adrenal tumor, Cushing syndrome and exogenous androgen use must be excluded.

It is recommended to measure free testosterone, serum TSH, prolactin, GnRH, DHEAS, 17-hydroxyprogesterone, and cortisol level for exclusion of other etiologies. A 2-hour GTT (Glucose Tolerance Test) is frequently used to exclude impaired glucose tolerance (IGT) and type 2 DM, and is particularly important in obese PCOS patients who are at higher risk for both.

Sonographic criteria for polycystic ovaries (2003 Rotterdam Conference) include 12 small cysts (2 to 9 mm in diameter) or an increased ovarian volume (>10 mL) or both. Often there is an increased amount of stroma relative to the number of follicles. Only one ovary with these findings is sufficient to define PCOS. However, criteria do not apply to women taking combination oral contraceptive pills.

In anovulatory infertility, ovarian wedge resection (OWR) was the therapy of choice until 1960s when clomiphene citrate was introduced. After the introduction of laparoscopy with electrocauterization of the ovaries, this procedure alone or in combination with clomiphene citrate or gonadotropins replaced OWR as a surgical option for ovulation induction. A study reviewed fertility and menstrual pattern in 149 PCOS patients 15-25 years after OWR. Regular menstrual pattern lasting up to 25 years after surgery was restored in 88% of the patients and their cumulative pregnancy/ live birth rate was 78%.

Metformin for the treatment of PCOS
The use of insulin-sensitizing medications such as metformin in the treatment of PCOS recently has become an area of great interest. Its use may reduce the risk of hyperinsulinism, type 2 diabetes, and metabolic syndrome. Reduction in hyperinsulinism also has been shown to induce ovulation and regulation of menstrual cycling. The use of metformin in young adolescents with PCOS may regulate menstrual cycling and reduce clinical hyperandrogenic effects.

Metformin is approved by FDA for use in patient 10 year-old and older with type 2 diabetes. However, metformin can cause gastrointestinal side effects, which may limit its use in some adolescents. This side effect is often temporary and can be mitigated by a slow escalation in dose to maximal tolerated dosage. Patients with impaired renal function, hepatic dysfunction, and possibly excessive binge drinking have an increased risk of lactic acidosis with the use of metformin and thus are not appropriate candidates for this therapy.

Metformin is becoming a first-line therapy in adults with PCOS, particularly those with documented insulin resistance. This therapy should be considered for appropriate adolescents with PCOS to reduce the risk of development of diabetes, improve menstrual functioning, and perhaps improve clinical and biochemical hyperandrogenism. The additional of oral contraceptive hormones or anti-androgen medications often is used in this population.

Metformin was supposed to prevent
Gestational Diabetes (GD) by protecting the reserve of pancreatic β-cells by reducing insulin resistance and through an effect on weight gain. Romualdi D et al concluded that their study does not confirm the reduction of GD occurrence in PCOS subjects undergoing metformin treatment throughout pregnancy. On the contrary, they observed a high rate of GD, in most cases, in an early phase of gestation. They adopted Carpenter and Coustan criteria, which consider lower threshold values for diagnosis and are able to identify up to 40% diabetic pregnant women who would be missed by National Diabetes Data Group criteria and thus would have developed of a higher rate of gestational complications.

Clomiphene Citrate (C/C) was the first agent used in experiments for ovulation induction in oligomenorrheic women. For many years it was and may still be the first therapeutic option managing anovulatory infertility. Treatment with C/C in anovulatory PCOS women is associated with an ovulation rate of 60-85% and a pregnancy rate of 30-40%.

The addition of metformin to C/C in C/C resistant women significantly improves ovulation rates. A meta analysis in a Cochrane review reported a significant benefit for metformin compared to placebo for ovulation in anovulatory women with PCOS. A recent review confirmed the superiority of metformin and C/C combination in the C/C resistant patient regarding ovulation and pregnancy rates. Contrary to this result, another study found no significant differences groups studied.

Administration of metformin to pregnant women with PCOS throughout pregnancy was associated with a marked and significant reduction incidence of early pregnancy loss. It is postulated that this was achieved by different potential metabolic, endocrine, vascular and anti-inflammatory benefits of metformin administration.

The thiazolidinediones are another class of medications also used for patients with diabetes mellitus and include rosiglitazone and pioglitazone. These agents bind to insulin receptors on cells throughout the body, causing them to become more responsive to insulin and thereby lowering serum glucose and insulin levels. Similar to metformin, rosiglitazone and pioglitazone have been shown to improve ovulation in some patients. A data show that both metformin and rosiglitazone improve ovarian function and hirsutism in patients with PCOS. However, rosiglitazone improve appears better than metformin in the treatment of hirsutism and has better patient tolerance.

Several combination therapies have been investigated for the treatment of adolescents with PCOS. Recommended combinations would include metformin plus oral contraceptive therapy, spironolactone plus oral contraceptive therapy, metformin plus spironolactone, or the use of all three medications.

SUMMARY

PCOS is a complex syndrome that includes clinical and biochemical evidence of hyperandrogenism and hyperinsulinism. Adolescents with PCOS are affected by both short-term and long-term consequences such as future fertility, which may affect psychological well being and health behaviours. In addition, patients with PCOS are at increased risk for development of insulin resistance, type 2 diabetes, metabolic syndrome, and cardiovascular disease. This at-risk group requires rigorous evaluation, treatment and long-term counseling and management by healthcare provider.

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