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Review Article

POLYCYSTIC OVARY SYNDROME (PCOS)–AN OVERVIEW

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ABSTRACT

Polycystic ovary syndrome (PCOS) is one of most common female endocrine disorder that affects 6-15% of the female population. Women with PCOS have a hormonal imbalance and metabolism problems that may affect their overall health and appearance. Androgen excess and insulin resistance are currently recognized to be responsible for much of the phenotypic presentation, though insulin resistance is far from universally present. It is characterized by irregular menstrual cycle, acne and also associated with type-2 diabetes mellitus and cardiovascular disease. Efficient management of PCOS provides a prospective window of opportunity to avoid the risk of associated complications. Treatment is broadly aimed at tackling (IR), effects of hyperandrogenism, irregular menstruation, and infertility. This review article mainly deals with the etiology, pathophysiology, diagnosis and management of polycystic ovary syndrome.

Keywords: Polycystic ovary syndrome, PCOS, Insulin resistance, Metformin

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorder that affects 6-15% of the female population [1]. It is primarily characterized by an extremely irregular menstrual cycle in which ovulation does not occur [2]. The major endocrine gland that involved in the PCOS are hypothalamus, pituitary gland, ovaries and adrenal gland and peripheral adipose tissue that together contribute to create a generally imbalance. Most symptoms first appear in adolescence around the start of menstruation. However, some women don`t develop symptoms until early-mid 20`s.[1] It is also known as Stein-Leventhal syndrome or hyperandrogenic anovulation (HA). It also referred to as syndrome "O" that is over nourishment, overproduction of insulin, ovarian confusion and ovulatory disruption [2]. It is associated with the development of type-2 diabetes and recurrent miscarriage [3].

A PCOS patient ovaries contains more than ten follicles visible on ultrasound. The polycystic ovary, in comparison to normal ovary, its layer has more follicle and has a dense centre. This centre is known as stroma which is where testosterone made [4]. Generally, PCOS consist of the presence of any 3 criteria, oligo-anovulation, clinical or biochemical evidence of hyperandrogenism and the presence of polycystic ovaries on ultrasound examination. However, polycystic ovaries are non-specific finding noted in women with no endocrine or metabolic abnormalities.[5] PCOS is one of leading cause of female subfertility and the most frequent endocrine problem in women of reproductive age. The cysts are not harmful but lead to hormone imbalances and cause problems of periods and make difficult to get pregnant.[6] PCOS is medical condition in which there is an imbalance of female sex hormones. That is, elevated levels of testosterone, DHEA-S, androstenedione, prolactin and LH along with normal, high or low estrogen levels. Hyperinsulinemia, insulin resistance and impaired glucose tolerance are very common in women with PCOS but insulin resistance may occur in lean women with PCOS [7] National Institute of Health (NIH), it was recommended that the diagnostic criteria for PCOS involve the concomitant presence of anovulation and evidence of hyperandrogenaemia [8].

In clinical practice, 75% of women with PCOS suffer from anovulation infertility and 50% of them experience recurrent pregnancy loss. However, it not clear whether these defects are caused by uterine dysfunction itself or by the interrupted interaction between uterine cells and developing embryo. Young women with PCOS induced endometrial hyperplasia are more likely than non PCOS women to develop endometrial carcinoma. The precise etiology and pathogenesis of PCOS remain uncertain [9] PCOS are commonly found by the use of ultrasound, magnetic resonance imaging (MRI) and computed tomography scanning (CT) [10].

Etiology

The exact cause of PCOS is unknown or heterogeneous in nature however it certainly linked to a variety of etiological factors [2].

Insulin resistance

PCOS is a multifaceted metabolic disorder that shows high association with insulin resistance leading the hyperinsulinemia, 10% show type-2 diabetes. 30-35% have impaired glucose tolerance (IGT). Result in increased production of testosterone lead to abnormal ovulation. Studies suggest that high activity levels of micro RNA in fat cell hinders the use of glucose by insulin contributing to PCOS and also insulin resistance [2]

Hyperinsulinemia is probably the result of both increased insulin secretion and a decrease in insulin clearance. Anovulatory women with PCOS are relatively hyperinsulinaemic and more insulin resistant than ovulatory women with PCOS [4] Selective insulin resistance is central to the etiology of PCOS. Thus compensatory hyperinsulinaemia may result in a decreased level of serum hormone binding globulin (SHBG), and serve as a trophic stimulus to androgen production in the adrenals and ovaries and have a direct effect on hypothalamus causing an abnormally stimulated appetite and increased gonadotropin secretion. It includes reduced insulin receptor activity peripherally and leads to endocrine dysfunction of PCOS.[5]Obesity amplifies the degree of insulin resistance and hyperinsulinaemia.[6]Insulin drives increased androgen production from the ovary and adrenal and may alter gonadotropin secretion. It is also responsible for decreased SHBG synthesis in the liver thus increasing free testosterone in the circulation. Ovarian insulin sensitivity to the prevailing hyperinsulinemia is thought to be one of the mechanisms that drives ovarian androgen production. Body mass index, hyperandrogenaemia, and clinical hyperandrogenism are independent predictors of insulin resistance [10]. Altered steroid negative feedback regulation of LH together with the compensatory hyperinsulinemia due to insulin resistance may disrupt ovulatory function, causing anovulation [8].

Hormonal imbalance: The imbalance of certain hormones is common in women with PCOS.

- High testosterone level leads to hyperandrogenism.
- High LH whose excessively increased levels of disrupt proper ovarian functions.
- Low sex hormone binding globulin (SHBG) that allow expression of hyperandrogenism.
- High prolactin level stimulates the production of milk in pregnancy, and it raised in few patients [2].

The exact reason of this hormonal imbalance is unknown.[2] Excess production of androgen is the most feature in women with PCOS. Although the adrenal may contribute to excess testosterone circulating in women with PCOS. The major source of excess androgen is the ovary. The LH will be higher in PCOS patient, the mechanism is not entirely clear, but the predominant reason is abnormal negative feedback on LH secretion mediated by either estradiol or progesterone [4] High serum concentration of androgenic hormones such as testosterone, androstenedione, and dehydroepiandrosterone sulphate (DHEA-S) occurred in patients [6] Occurrence attribute to enhanced serine phosphorylation unification theory lead to increased CYP17 activity in ovary (hyperandrogenism) [5]. Hypothalamic-pituitary axis (HPA) abnormalities cause abnormal secretion of gonadotropin-releasing hormone (GnRH) and LH, resulting in increased ovarian androgen production. LH stimulates the theca cell in the ovary to synthesis androgens, and FSH is responsible for the granulosa cell synthesising oestrogen via its action on aromatase activity. Increased GnRH pulse frequency favours increased LH levels. Women with PCOS tend to have increased LH: FSH ratios [11].

Genetic factors

PCOS is a genetically determined ovarian disorder. Excessive exposure to androgens during intrauterine life have a permanent effect on gene expression leading to PCOS and later to insulin resistance. PCOS is genetically determined ovarian disorder and the heterogeneity explained on the basis of interaction of the disorder with other genes and with environment[2]. However, it is unlikely that PCOS represents a single gene defect and it is more likely to be polygenic or oligogenic on the other hand, low birth weight and foetal exposure to androgens contribute to the development of PCOS phenotype [8]

Bisphenyl A (BPA)

Bisphenyl, a common industrial compound used in dentistry, plastic consumer products, and packaging to be a probable cause of PCOS. BPA has a role in ovarian dysfunction [2]

Stress and other psychological disorders

PCOS often caused by psychological disorders. Increased stress can upset the normal menstrual cycle and cause hormonal change such as raised level of cortisol and prolactin that affect menstruation that normally resumes after the stress subsides [2]

Ovarian follicular defect

Women with PCOS have 2-6 fold more primary, secondary and small anteal follicles when compared to normal ovaries. Abnormal androgen signaling is responsible for the increase in follicle number, and also follicles grow very slowly due to possibly deficient growth signals from the ovary [11].

Miscellaneous

The sedentary lifestyle, dietary vacations, lack of exercise or intensive physical exercise and also contributory factors such as extreme weight loss, disorders of the endocrine system and various disorders of the ovaries [2].

Clinical manifestations

- Hyperandrogenism-characterized by elevated levels of serum androgen.
- Anovulation.
- Metabolic disturbances.
- 15% of females having irregular menstrual cycles.
- Chronic anovulation [3]
- Hyperinsulinemia and decreased levels of SHBG [5].
- Menstrual disorders: PCOS mostly produces oligomenorrhea (few menstrual periods) or amenorrhea (no menstrual periods).
- Infertility: due to chronic anovulation.
- High levels of masculinizing hormones: the most common signs are acne and hirsutism but it may produce hypermenorrhoea (heavy and prolonged menstrual periods), androgenic alopecia (increase hair thinning or diffuse hair loss).
- The severity of any of these manifestations is highly variable and may depend on genetic and ethnic differences in the sensitivity to the effects of androgen [6].
- Weight gain and obesity.
- Male pattern baldness.
- Patches of thickened and dark brown or black skin on the neck, arms, breast and thigh.
- High BP.
- Pelvic pain [12]
- Symptoms including oligo-ovulation, biochemical or clinical hyperandrogenism, polycystic ovaries and hyperinsulinemia [13].

Pathophysiology

Several theories have been proposed to explain the pathogenesis of PCOS:

- Endometrial progesterone resistance
- A unique defect in insulin action and secretion.
- A primary neuroendocrine defect leading to an exaggerated LH pulse frequency and amplitude.
- A defect of androgen synthesis that results in enhanced ovarian androgen production.
- An alteration in cortisol metabolism resulting in enhanced adrenal androgen production [14].

Endometrial progesterone resistance

Endometrial responsiveness to progesterone is reduced in women with PCOS and a study shown that total endometrial progesterone receptor expression is higher in women with PCOS. Increased progesterone receptor expression in epithelial cells is greater than that in stromal cells in women with PCOS, suggesting the lower binding of progesterone in stromal cells [9].

Disorders starting in childhood indicate a genetic component pubertal onset may be temporary for up to 2 y. Onset after marriage indicates stress and obesity. And onset away from the physiological point indicate a tumor. Sclerocystic ovaries follow pelvic infection by 6-18 mo [10].

Insulin resistance

It is the reduced glucose response to a given amount of insulin. Insulin resistance is a common feature of both obese and non-obese women. In addition to insulin resistance, pancreatic beta-cell secretory dysfunction has been reported in PCOS. Cell defect-increased secretion of insulin under basal condition and decreased secretion after meals [14].

There are two important actions of insulin which contribute to hyperandrogenism in PCOS.

❖ Inhibition of hepatic synthesis of serum sex hormone binding globulin (SHBG).

❖ Inhibition of hepatic production of IGFBP-1 which allows an increased level of IGF-1 and greater local activity [14].

Neuroendocrine defect

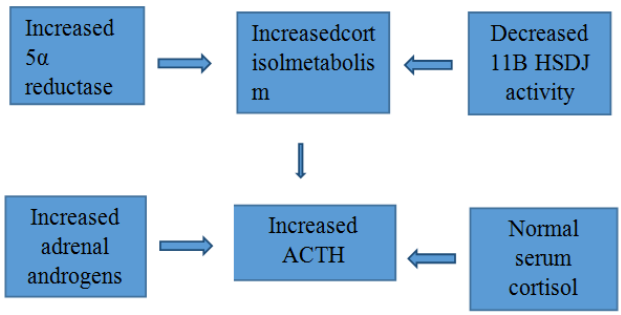
LH hypersecretion is considered to be the primary abnormality in classic PCOS and thus cause of androgen excess [14].

Ovarian defect

PCOS as a form of gonadotropin-dependent ovarian hyperandrogenism in which the central abnormality is an elevated intraovarian androgen concentration. PCOS patients have increases formation of 17α hydroxyprogesterone and androstenedione in response to LH [14].

Increased peripheral cortisol metabolism

An increased androgen production found in 25% of PCOS women as a result of a genetic trait or secondary to ovarian hormonal secretion. This involves irreversible inactivation of 5α reductase and 5β reductase in the liver and reversible interconversion with cortisone by 11βHSD in the liver and adipose tissue [14].



Polycystic ovary syndrome is extremely common disorder effecting 4%-12% of women of reproductive age on average, the normal ovary contains 5 follicles and is about the size of a walnut. Polycystic ovary contains more than 10 follicles. The increased size of polycystic ovary is due to increased amount of stroma.[1]PCOS characterized by hyper stimulation of pituitary by LH, which result in anovulation, multiple cysts and excess androgen output. Elevated LH level can be used as a marker in predicting the risk of miscarriage [3].

Raised insulin and this proportion raise in those who are overweight [4]. PCOS is that it is a partial resistance which involves metabolic activities of insulin but does not prevent insulin effect on its receptors on the ovary. The main effect of insulin on the ovaries is not only increased androgen production but also derange the regulation of androgen synthesis so it prevents the down-regulation of LH receptors leading to increased production of androgens and oestrone which coupled with insulin effect lowering SHBG leads to hyperestrogenism and decreased FSH levels [5]. Hyperinsulinemia may also result in suppression of hepatic generation of sex hormone binding globulin (SHBG) which in turn increases androgenicity [6].

In women with PCOS there will be an imbalance between FSH which stimulate the ovary to develop an egg, it ripens but does not rupture. Instead, it starts accumulating in ovaries. By this time, LH level increases egg may start to grow and remain as cyst in the ovary as the result occultation does not takes place. Unruptured follicles produce testosterone [12].

Androgen produced during differentiation are potent gene transcription factors induce other critical transcription factors interact with its own receptor in foetal tissues enhancing gene expression later manifest the phenotype of PCO[15]. Animal studies have shown that exposure to androgens in pregnancy induces PCOS like syndrome and a similar effect in human can only be postulated [11].

PCOS is often characterized by the presence of insulin resistance and associated hyperinsulinemia and most the patient in clinical series are overweight or obese. These factors play an important role in the pathogenesis of androgen excess and the susceptibility to develop earlier than expected glucose intolerance states and type-2 diabetes (T2DM) [1].

Diagnosis

Polycystic ovary syndrome is difficult to diagnose due to the intrinsic characteristics of the syndrome: the heterogeneity of the symptoms; their variability in different age ranges[1]. PCOS is difficult or impossible to diagnose in adolescent and menopausal women because the puberty mimics the signs and symptoms of polycystic ovary syndrome. Menarche is also the appearance of multiple small antral follicles, and it is very easy to confuse. In menopausal women, the recall of menses is highly inaccurate and also on the basis of biochemical hyperandrogenaemia [16].

PCOS is marked by oligomenorrhea or amenorrhea, infertility and the presence of cystic ovaries, which is initially identified on laparotomy and confirmed by biopsy. Transabdominal 2-D ultrasound (TAUS) has largely been superseded by (TV) scanning because of greater resolution and in many cases patient preference. The transabdominal scan offers a panoramic view of the pelvic cavity, and it may be useful if any associated uterine or ovarian developmental abnormalities are present. Transvaginal scan has greater resolution and gives a more accurate view of the internal structure of ovaries especially in obese women. The ultra-sonographic examination allows evaluating both external and internal ovary aspects.

One of the most immediate common symptoms of PCOS is the excess of androgens (hyperandrogenism) which is diagnosed by laboratory investigations, that is, by looking for increased serum levels of androgens, or through clinical examination.[1]

PCOS has undergone many iterations of diagnostic criteria: [2]

- Criteria of the National Institute of Health (NIH) 1990:-
  - Chronic anovulation
  - Clinical and biochemical and hyperandrogenism
- Rotterdam criteria 2003:-
  - Oligo or anovulation
  - Clinical or biochemical signs of hyperandrogenism
  - Polycystic ovaries in imaging
- AES criteria 2009:-

Hyperandrogenism including hirsutim and or hyperandrogenaemia. Ovulatory dysfunction including oligo or anovulation and or PCO exclusion of any other androgen excess or related disorders.

- Ovulation morphology on ultrasound or polycystic ovaries: -

The inclusion of ultrasonographic evidence of PCO morphology is controversial.

- Hyperandrogenism: -

Determination of HA in females can be problematic during clinical and biochemical assessment.

- Menstrual dysfunction with oligo/anovulation: -

The absence of menstruation for a period of 45days or more and or 8 or menstrual cycles per year are also important diagnostic signs. Oligomenorrhea is considered as a highly predictive surrogate machee of PCOS. Additional characteristics are excessive hair growth, abnormal bleeding, obesity, hair loss, acne and infertility.

- Recent diagnostic parameters;

Antimullerian hormone [AMH] levels proposed as a parameter to replace ultra-sonographic assessment. Another diagnostic parameter is an assessment of ovarian stromal volume, measured as a ratio of stromal area to the total area of the ovary (S/A ratio) [2].

A physical examination is measuring blood pressure, weight and height should be completed. A routine and general physical examination should also have conducted and note the presence of secondary sex characteristics, along with palpation of thyroid gland for masses or enlargement.

Further diagnostic information can be obtained through laboratory measurement of FSH, LH, thyroid-stimulating hormone, prolactin, dehydroepiandrosterone and testosterone levels to detect the exact hormonal imbalance. Total cholesterol and HDL also obtained [3].

The presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and or increased ovarian volume (10 ml) which is obtained by sonography [4].

- Differential diagnosis: [5]

The clinician must consider several possibilities including:

- Exogenous androgens.
- Androgen secreting tumours.
- Acromegaly.
- Cushing's syndrome.
- Primary ovarian failure.
- Thyroid dysfunction

- Diagnostic evaluation and work-up: -

- Routine physical examination.
- BMI->30 is obese.
- BP recording.

- Laboratory investigations: -

- Demonstration of biochemical hyperandrogenaemia.
- S: estradiol and FSH estimations.

- Laparoscopy: [6]

- Many patients with PCOS, particularly those who are having trouble becoming pregnant will have a laparoscopy.
- In laparoscopy operation, the patient receives a short general anaesthetic; a small cut is made in the umbilicus and a telescope is inserted to look at the pelvic contents including the uterus, tubes and ovaries. The ovaries are look like ping-pong balls.

- Hysteroscopy: -

- In hysteroscopy operation, a fine telescope is used to look inside the cavity of womb. it is used for patients those who have abnormal bleeding [6].

Oestrone: -Serum androgen concentrations have little attention in diagnosis [8].

Vitamin D: -Deficiency of vitamin D is common in women with PCOS. Especially in obese ones. Its deficiency also affect fertility in women with PCOS [8].

Complications

PCOS it produces further complications, with the hyperoestrogenic environment converting ovarian and adrenal androgens to oestrone peripheral fat cells [3]. Women with PCOS have enhanced risks of ovarian hyper stimulation, multiple pregnancy, and first trimester pregnancy losses. All are associated with endometrial cancer in later years [5]

Management

There is no treatment which reverses the hormonal disturbances of PCOS and treats all clinical features, so medical management is targeted at individual symptoms, and only in association with life style changes [4]

Life style management of PCOS [2]

- Diet regimen:

Diet regimen not only aims at weight management but also prevents long term risk of PCOS. Type-2 diabetes mellitus, cardiovascular disease etc…

The following products should be avoided:

- Alcohol, caffeine, nicotine and their addictive agents.
- Soy products-as they impede ovulation.
- Milk-protein limits normal testosterone processing causing level storise.
- Saturated fats-red meat, dairy products as they increase oestrogen production.
- High glycaemic index such as white rice, potatoes.

The following products should be consuming:

- Whole grains-ragi, red rice.
- Green leafy vegetables-rich minerals, vitamins and nutrients.
- Dry fruits-dates, fig.
- Low glycaemic whole fruits-apples, pears, grapes, oranges and plums.
- Bright coloured vegetables-carrots, capsicum, beets, salad etc…
- Carbohydrates and proteins.

Exercise: -10 min' exercise improve the condition of PCOS.

Pharmacological management

Clomiphene citrate

It is used as first-line treatment for ovulation induction in PCOS patients. It is the oestrogen receptor antagonist that interfere with negative feedback of oestrogensignaling pathway resulting in increased availability of FSH. Increased FSH leads to follicular growth [4]. It takes in the first part of menstrual cycle [6]. It is also used to treat infertility [16].

Metformin

Insulin sensitizing agents such as metformin, troglitazone are antagonize some hyperandrogenic signs, by reducing total and free testosterone concentration [1]. It increases ovulation and reduces the problem caused by insulin resistance and regulates excessively raised levels of androgens.[2] It restores menstrual cycle, ovulation and fertility [3]. Short term treatment of 3-6 mo of metformin in PCOS to improve ovulatory functions and circulating androgen is fall [5]. During pregnancy, it reduces number of pregnancy related problem such as gestational diabetes and gestational hypertension [7].

Flutamide

It proposed as alternative to spironolactone, which act by inhibiting the androgen receptor.[3] It is the non-steroidal pure antiandrogen which inhibit the androgen receptor in a dose dependent manner and not having better efficacy than spironolactone [10].

Glucocorticoids

Prednisone and dexamethasone have been used to induce ovulation. In PCOS patients with high adrenal androgen, low dose dexamethasone (0.25-0.5 mg) at bed time can be used [4].

Gonadotropins

It is used as second line of therapy after resistance to clomiphene citrate. It induces ovulation, maintain and provoke optimum follicle growth with the controlled administration of FSH[4] and its treatment started with low doses [5]

N-acetyl-cysteine (NAC)

It has antioxidant required for the body's production of glutathione which inhibit the oxidative stress and prevention of hyperinsulinaemia [17].

Surgery

Laparoscopic ovarian drilling (LOD) which is used in patients who do not respond to clomiphene therapy, it destroys androgen producing tissues. Correcting in hormonal imbalance and restoring

ovarian functioning. Treatment include suppression of hyperandrogenism to improve acne and hirsutism [2].

Therapy for hirsutism

Cosmetic hair removal

Cosmetic removal include temporary such as tweezing, shaving, waxing and depilatories, while electrolytes and laser treatment will remove hair permanently. This treatment should not be started until 6 mo after the start of medical therapy [3].

Pharmacotherapy

The pharmacological treatment of hirsutism slows the growth of new hair but does not affect established hair. Reduction of testosterone to a normal level can be finished by ovarian suppression with 100-200 mg spironolactone daily [3].

CONCLUSION

PCOS is common endocrine disorder in premenopausal women. It is characterized by irregular menstrual cycle, acne and also associated with type-2 diabetes mellitus and cardiovascular disease. The fundamental defect of PCOS remain unknown. Lifestyle modification along with pharmacological therapies that improve hyperandrogenism and improve insulin sensitivity, assisting regular menstrual cycle and increased fertility and preventing cardiovascular and other consequences.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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