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Unraveling The Complexity Of Polycystic Ovary Syndrome (PCOS) : A Comprehensive Review Of Etiology, Diagnosis, And Management Strategies

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Abstract:

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 6-15% of women worldwide. Its etiology involves insulin resistance, hyperandrogenism, obesity, hormonal imbalances, genetic factors, environmental exposures, stress, and ovarian follicular defects. PCOS significantly impacts women's quality of life and mental well-being. Management strategies should address these multifactorial aspects, including lifestyle interventions for obesity and hormonal balance. A better understanding of PCOS complexities can improve reproductive and metabolic outcomes for affected women.

Keywords: **Hyperandrogenism, Follicular Defects, Endocrine, Multifactorial.**

1.INTRODUCTION:

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders that affect 6-15% of the female population. Polycystic ovary syndrome (PCOS) is a frustrating experience for women, often complex for managing clinicians. A major endocrine disorder in young age women affecting their health-related quality of life (HRQOL) and their mental well-being as well, this develop into lifelong health condition that continues far beyond the young age(1).

A heterogeneous endocrine disorder distinguished by the manifestation of ovarian cysts, anovulation, and endocrine variation that severely impact the life of a woman, The disturbance in the reproductive hormones like LH, FSH, estrogen, testosterone interrupts the normal menstrual cycle and would lead to oligomenorrhoea, amenorrhea like irregularities(2). It is primarily characterized by an extremely irregular menstrual cycle in which ovulation does not occur.

2.EPIDEMIOLOGY:

According to the World Health Organization (WHO) estimation revealed over 116 million women (3.4%) are affected by PCOS worldwide (Bharathi et al., 2017)(3). a study conducted at Oxford University and a private medical center, a 6.8% prevalence of PCOS was estimated. PCOS affects 1.55 million women of reproductive age worldwide, resulting in 0.43 million disability-adjusted life years (DALYs)(4).

PCOS is a common endocrinopathy affecting 4%–8% of women of reproductive age.

The prevalence of PCOS depends on the choice of diagnostic criteria. Most prevalence studies in India and recently a few studies among adolescents in schools report prevalence of PCOS as 9.13% to 36%(5). According to the World Health Organization (WHO), 116 million women worldwide suffer from PCOS(6).

3.ETIOLOGY:

1. insulin resistance and hyperandrogenism
2. Impact of obesity on polycystic ovary syndrome
3. Hormonal imbalance
4. Genetic factors
5. Bisphenyl A (BPA)
6. Stress and other psychological disorders
7. Ovarian follicular defect

1. insulin resistance and hyperandrogenism : the underlying hormonal imbalance created by a combination of increased androgens and/or insulin underpin PCOS. Hyperandrogenism is a well established contributor to PCOS aetiology, detected in around 60% to 80% of cases. Insulin resistance is a pathophysiological contributor in around 50% to 80% of women with PCOS , especially in those with more severe PCOS diagnosed on National Institutes of Health (NIH) criteria and in women who are overweight(7,8). Insulin resistance contributes to metabolic features but also to reproductive feature through augmenting androgen production and increasing free androgens by reducing sex hormone binding globulin (SHBG)(9).

   Hyperinsulinemia is probably the result of both increased insulin secretion and a decrease in insulin clearance (10).
2. Impact of obesity on polycystic ovary syndrome: Obesity increases hyperandrogenism, hirsutism, and infertility and pregnancy complications both independently and by exacerbating PCOS. Obesity and insulin resistance further increase type 2 diabetes (DM2) and cardiovascular disease (CVD). Women with PCOS have increased risk factors for DM2 and CVD, increased impaired glucose tolerance (IGT), DM2 and potentially increased CVD. Treatment of obesity through lifestyle intervention is a key treatment strategy in PCOS and improves insulin resistance, reproductive and metabolic features(9).
3. Hormonal imbalance: 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 serum concentration of androgenic hormones such as testosterone, androstenedione, and dehydroepiandrosterone sulphate (DHEA-S) occurred in patients. Occurrence attribute to enhanced serine phosphorylation unification theory lead to increased CYP17 activity in ovary (hyperandrogenism). Hypothalamic-pituitary axis (HPA) abnormalities cause abnormal secretion of gonadotropin-releasing hormone (GnRH) and LH, resulting in increased ovarian androgen production(11,12).

4. Genetic factors: Excessive exposure to androgens during intrauterine life has a permanent effect on gene expression leading to PCOS and later to insulin resistance. 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. PCOS is genetically determined ovarian disorder and the heterogeneity explained on the basis of interaction of the disorder with other genes and with environment.
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6. Stress and other 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(16,17).
7. Ovarian follicular defect: 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(10).

4.Clinical features:

- Hyperandrogenism-characterized by elevated levels of serum androgen.
- Anovulation.
- Metabolic disturbances.
- Chronic anovulation
- Hyperinsulinemia and decreased levels of SHBG.
- 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 (10).
- 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
- Symptoms including oligo-ovulation, biochemical or clinical hyperandrogenism, polycystic ovaries and hyperinsulinemia(10).

5.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.
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(10).

1. Pelvic Exam: checks the uterus, inspects the uterus for masses, growth, or other abnormalities.
2. Blood test: hormone levels, triglycerides, 25-hydroxy Vit D3, FSH, serum luteinising hormone, testosterone, estradiol, 17-OH progesterone, TSH, and serum prolactin
3. Ultrasound: to check the size and appearance of ovaries and the thickness of the uterus lining.

The ultrasonographic examination allows evaluating both external and internal ovary aspects.
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(10).

5.1**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)(10).
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(18).

Additional tests for complications after being diagnosed with PCOS:

- Regular checks of blood pressure, glucose tolerance, and cholesterol and triglyceride levels.
- Screening for obstructive sleep apnea.
- Screening for depression and anxiety.

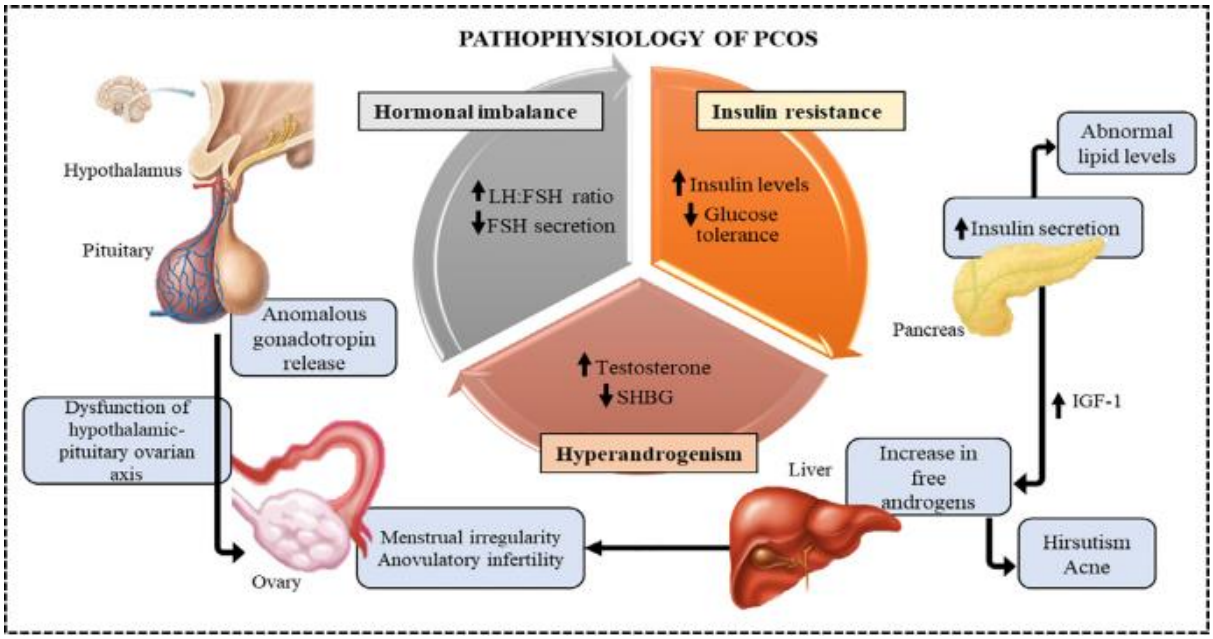
Blood tests can be used to identify characteristic changes in hormone levels, although these changes are not universal. Women with polycystic ovary syndrome may have elevated levels of:

- Testosterone (an ovarian androgen hormone that influences hair growth);
- Oestrogen (an ovarian hormone that stimulates growth of the womb lining (endometrium);
- Luteinising hormone (LH, a pituitary hormone which influences hormone production by the ovaries and is important for normal ovulation);
- Anti - müllerian hormone (which is measures the fertility level of the ovaries)(7).

6.Pathophysiology:

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

1. Endometrial progesterone resistance
2. A unique defect in insulin action and secretion.
3. A primary neuroendocrine defect leading to an exaggerated LH pulse frequency and amplitude.
4. A defect of androgen synthesis that results in enhanced ovarian androgen production.
5. An alteration in cortisol metabolism resulting in enhanced adrenal androgen production(19).



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6.1 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.

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 months(10).

6.2Insulin resistance: A unique defect in insulin action and secretion.

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 defectincreased secretion of insulin under basal condition and decreased secretion after meals(20). 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(21).

6.3Neuroendocrine: A primary neuroendocrine defect leading to an exaggerated LH pulse frequency and amplitude(22).

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

6.4Ovarian defect: A defect of androgen synthesis that results in enhanced ovarian androgen production.

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(21).

6.5Increased peripheral cortisol metabolism:

An alteration in cortisol metabolism resulting in enhanced adrenal androgen production. 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(21).

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.
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)(23).

7.Complications:

PCOS it produces further complications, with the hyperoestrogenic environment converting ovarian and adrenal androgens to oestrone peripheral fat cells. 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(24).

8.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 (25).

8.1 Life style management of PCOS:

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:

1. Alcohol, caffeine, nicotine and their addictive agents.
2. Soy products-as they impede ovulation.
3. Milk-protein limits normal testosterone processing causing level storise.
4. Saturated fats-red meat, dairy products as they increase oestrogen production.
5. High glycaemic index such as white rice, potatoes. The following products should be consuming:
6. Whole grains-ragi, red rice.
7. Green leafy vegetables-rich minerals, vitamins and nutrients.
8. Dry fruits-dates, fig.
9. Low glycaemic whole fruits-apples, pears, grapes, oranges and plums.
10. Bright coloured vegetables-carrots, capsicum, beets, salad etc…
11. Carbohydrates and proteins. Exercise: -10 min' exercise improve the condition of PCOS(26).

8.2 Pharmacological management:

1.Clomiphene citrate:

It is used as first-line treatment for ovulation induction in PCOS patients. It is the oestrogen receptor antagonist that interferes with negative feedback of oestrogen signaling pathway resulting in increased availability of FSH. Increased FSH leads to follicular growth. It takes in the first part of menstrual cycle. It is also used to treat infertility(27).

2.Metformin:

Insulin sensitizing agents such as metformin, troglitazone are antagonize some hyperandrogenic signs, by reducing total and free testosterone concentration . 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 [37]. 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(28).

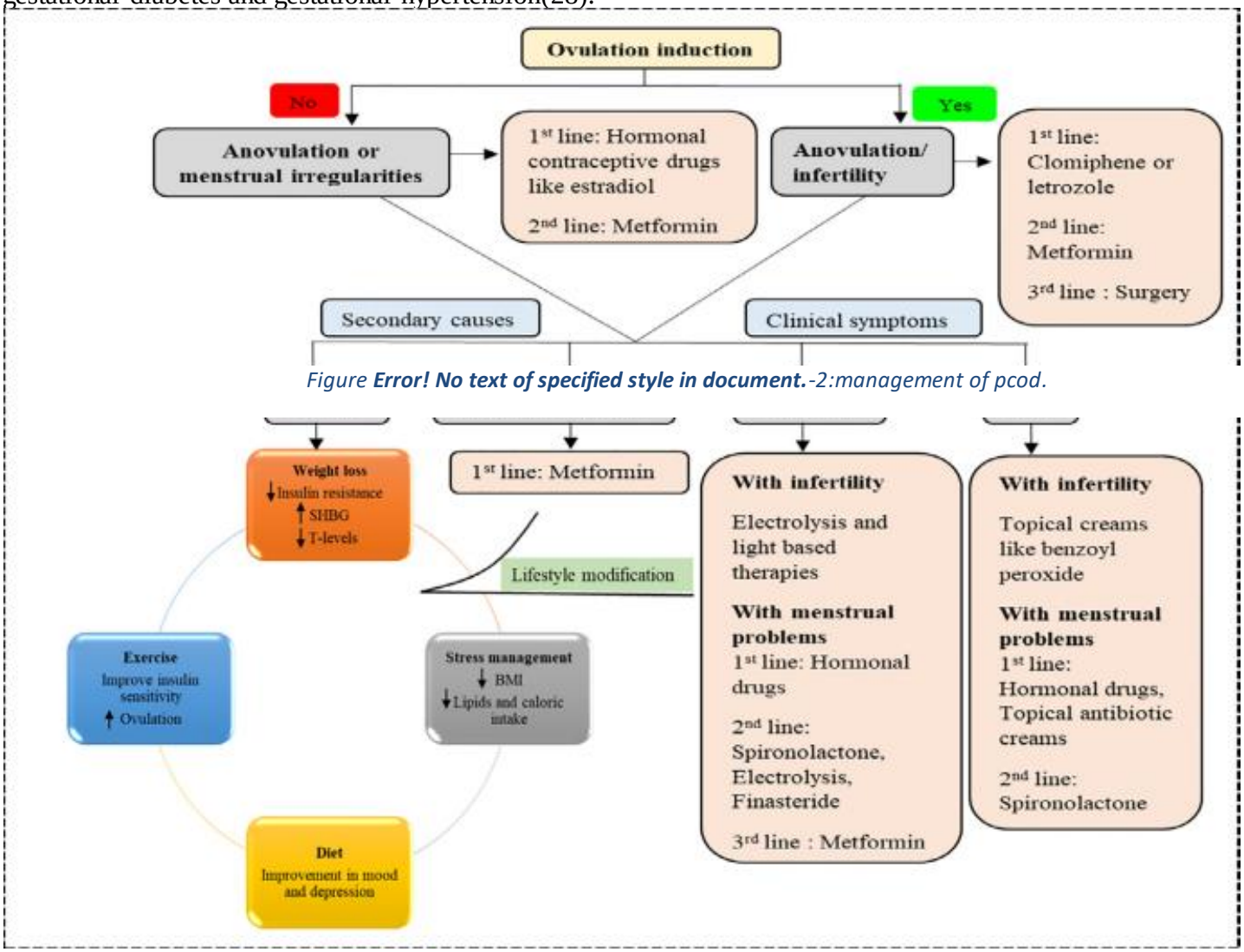

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figure 2:management od pcod

3.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(29).

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 FSH4 and its treatment started with low doses(24).

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(30).

6.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

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 month after the start of medical therapy(31).

8.3 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(31).

9.CONCLUSION:

PCOS is common endocrine disorder in premenopausal women. It is characterized by irregular menstrual cycle, acne and associated with type-2 diabetes mellitus and cardiovascular disease. The fundamental defect of PCOS remains 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.

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