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A Comprehensive review on criticalappraisal & pathogenesis of PCOS

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is a complex endocrine disorder affecting reproductive-aged women, characterized by clinical manifestations such as hyperandrogenism, menstrual irregularities, andpolycystic ovaries. According to World Health Organization (WHO) estimation revealed over 116 million women (3.4%) are affected by PCOS worldwide.

Symptoms of PCOS arise during early pubertal years. The predisposing risk factors include genetics, neuroendocrine, lifestyle/environment, obesity that contributes to the development of PCOS. The pathophysiology aspect of PCOS mainly focuses on hormonal dysfunction leading to impaired folliculogenesis which arise the risk for associated commodities like endometrial cancer and type II diabetes. This review highlights a brief overview of risk and pathophysiology treatment with drugs acting on infertility plus clinical symptoms of PCOS.

Keywords : Hyperandrogenemia, hyperandrogenism, insulin resistance, metabolic syndrome, polycystic ovary

I. INTRODUCTION

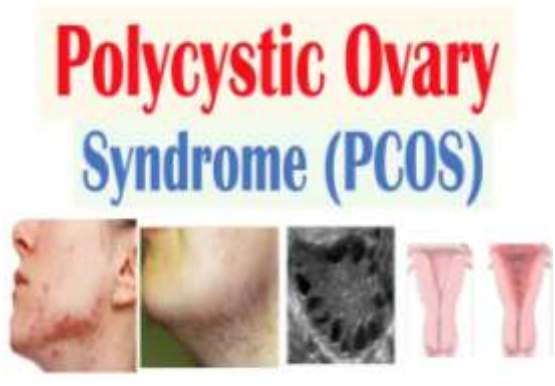
Polycystic ovarian syndrome (PCOS) is the most common endocrine pathology in females of reproductive age worldwide. Stein and Leventhal initially described the problem in 1935. The prevalence ranges between 5% and 26% [1], depending on the diagnostic criteria applied. Basing the clinical diagnosis of PCOS on the presence of at least 2 of the following 3 criteria is widely accepted among specialty society guidelines: chronic anovulation, hyperandrogenism (clinical or biochemical), and polycystic ovaries. PCOS is a diagnosis of exclusion, and disorders that mimic the clinical features of PCOS must be excluded.

Multiple comorbidities that areassociated with PCOS include infertility, metabolic syndrome, obesity, impaired glucose tolerance, type 2 diabetes mellitus, cardiovascular disease, depression, obstructive sleep apnea (OSA), endometrial cancer, and metabolic dysfunction-associated steatotic liver disease (MASLD).[2][3][4] Healthcare professionals need to be aware of the heterogeneity in prevalence across ethnicities, phenotypic presentations, and pathogenetic mechanisms.

Symptoms

Often, women and health care providers may not suspect PCOS because the symptoms may seem unrelated. These can include[5][6]

- Menstrual irregularities
- Infertility
- Increased hair growth on the face, chest, belly, or upper thighs—a condition called hirsutism
- Severe, late-onset, or persistent acne that does not respond well to common treatments
- Insulin sensitivity
- Obesity, weight gain, or trouble losing weight, especially around the waist
- Oily skin
- Patches of thickened, dark, velvety skin—a condition called acanthosis nigricans



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Symptom management is important, as the effects of PCOS can put you at **risk for complications** or long-term health problems

These factors lead to the cause of hyperinsulinemia, hyperandrogenism, oxidative stress, irregular periods eventually upsurging the metabolic syndrome[7]. PCOS was named so because it indicated multiple ovarian cysts (undeveloped follicles) on ultrasound examination. The follicles evolved from primitive follicles, but due to disrupted ovarian function, the development ceased at an early stage[8].

Etiology:

PCOS is a complex, multigenic disorder with strong epigenetic factors associated with it.[9] Genome-wide association studies (GWAS) have identified multiple PCOS-associated genetic loci; many of these genes are involved in various levels of insulin resistance, ovarian steroidogenesis, steroid hormone biosynthesis, PI3K-Akt signaling pathway, adrenal cortisone reductase deficiency, and gonadotrophic dysregulation.[10] Twin studies have estimated that about 70% of PCOS pathogenesis is attributable to genetic components.[11]

The DENND1A (Differentially Expressed in Normal and Neoplastic Development isoform A1) gene was identified as a potential risk marker.[12] Epigenetic factors like obesity affect the hypermethylation of granulosa cells in the ovary, inhibiting gene expression. Some hypotheses also include fetal androgen exposure as a potential etiology that requires validation.[13] The role of microRNAs in the regulation of GLUT4 implicated in insulin resistance has also been validated.[14][15]

Pathophysiology

The hormones that play a role in PCOS are:

- Androgens (like testosterone and androstenedione).
- Luteinizing hormone (LH).
- Follicle-stimulating hormone (FSH).
- Estrogen.
- Progesterone.
- Insulin.

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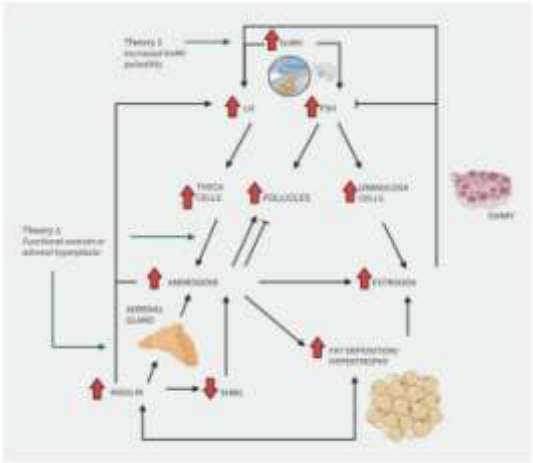

Pathogenesis of insulin resistance in polycystic ovary syndrome

Genetics and foetal origin

PCOS is an autosomal dominant genetic disease with various expression patterns that begins in early life, and metabolic changes precede reproductive abnormalities. It is characterized by higher BMI and glucose and insulin levels with relatively low SHBG and LH levels. IR is one of the prominent phenotypic characteristics of PCOS [16].

PCOS is associated with specific gene mutations, and most gene variants identified in genome-wide association studies are involved in regulating sheath steroid production, follicular maturation, or insulin signalling through the modified proteins they encode, such as insulin receptors, LH/HCG receptor activators, cell traffic proteins, and transcription factors [17, 18]A meta-analysis showed that the Gly972Arg polymorphism in insulin receptor substrate 1 (IRS-1) mediates the pathogenesis of PCOS by increasing fasting glucose levels and is a risk factor for susceptibility to PCOS [19, 20]. However, the genetic assessment of insulin-related genes is affected by the diagnostic criteria and genotyping methods employed with patients. [21]. Exposure to adverse intrauterine environments can lead to varying degrees of IR and HI. Exposure to dihydrotestosterone and insulin in the second trimester of pregnancy produces a PCOS-like phenotype and increases the risk of miscarriage [22]. Intrauterine growth restriction can affect foetal insulin secretion, and insulin resistance trends in PCOS may be involved in developmental origin and preprogramming as a nutritional compensation mechanism [23, 24]. Adolescents and young women with a history of low birth

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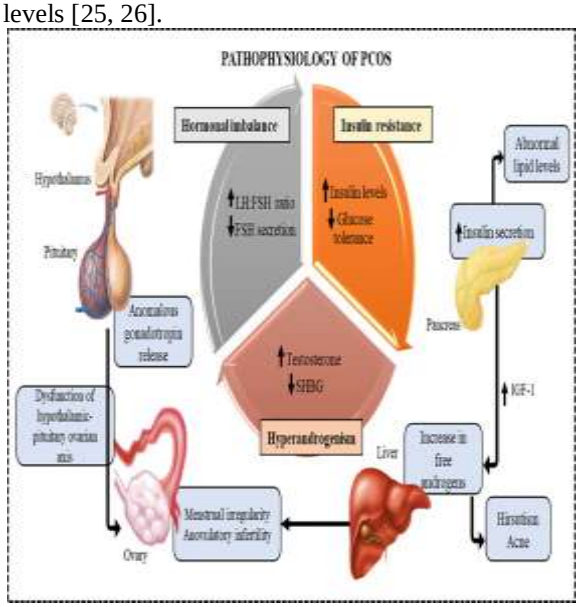
weight are more likely than normal women to have PCOS-like manifestations of IR and high androgen levels [25, 26].



Schematic depiction of PCOS linked mechanism. (Walters et al., 2018, Barber et al., 2016, Rojas et al., 2014).

Abbreviations - IGF-1- insulin-like growth factor, LH-luteinizing hormone, FSH-follicle stimulating hormone.

Clinical features of PCOS

The Clinical features of PCOS commonly includes acne, hirsutism, alopecia, acanthosis nigricans, skin tags and occasionally, darkening of complexion with weight gain.

If irregular menstrual cycles or primary infertility are the main complaints, the patient may consult a gynaecologist.

An alert clinician should be able to link the symptoms together, pointing to a possible underlying defect of hyperandrogenism[27].

Diagnosis

During this meeting, experts in the field once again endorsed the adoption of the more comprehensive 2003 Rotterdam criteria and proposed the identification of sub-phenotypes within such criteria, including[28]

1. Ovulatory dysfunction and androgen excess
2. Polycystic ovary morphology (PCOM) and androgen excess
3. PCOM and ovulatory dysfunction
4. PCOM, ovulatory dysfunction, and androgen excess.

3. Current recommendations

The differential diagnoses for PCOS include the following:

- Use of androgenic steroids
- Hypothyroidism
- Late-onset congenital adrenal hyperplasia
- Idiopathic/familial hirsutism
- Ovarian malignancies

Prevention

There's no proven way to prevent PCOS, but you can take small steps to reduce your symptoms. For example, eating nutritious foods, exercising regularly and managing a healthy weight for your body can help you avoid the effects of PCOS.

Treatment / Management

- Lifestyle Modification

Lifestyle modifications are the primary and most effective management approach for PCOS treatment. Lifestyle interventions, eg, exercise alone or a combination of diet, exercise, and behavioral strategies, should be recommended for all women with PCOS to reduce their metabolic dysfunction. [29]

- **Pharmacological Management**
- Hormonal contraceptives

The first-line treatment for women with symptomatic PCOS, specifically for issues such as menstrual irregularities, hirsutism, and acne, is a combined hormonal contraceptive. This can be administered as an oral contraceptive pill (OCP), patch, or vaginal ring.[29]

When prescribing oral contraceptives, an initial dosing of 20 µg of ethinyl estradiol combined with a progestin that has antiandrogenic properties, eg, desogestrel or drospirenone, or one with neutral effects like norethindrone acetate, is recommended. [30]On the other hand, a combination of metformin and low-dose spironolactone has been found to be more effective in alleviating symptoms and improving medication compliance than either medication used separately.[31]

- Metformin

Metformin improves menstrual cycles, abnormal waist-to-hip ratio, and vascular markers in nonobese women with PCOS.[32]

In adult women with PCOS, metformin may be less effective in improving hirsutism compared to OCPs in the subgroup with a BMI of

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25 kg/m^2 to 30 kg/$m^{2.}$ Metformin alone or OCP alone may be less effective in improving hirsutism than when metformin is combined with OCP.

- Infertility Treatment

The first-line therapy for infertility in PCOS patients is letrozole. Clomiphene citrate combined with metformin could be used rather than clomiphene citrate alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and clinical pregnancy rates.[29]

Additional Insulin Sensitizing Treatment in PCOS

- GLP-1 agonists

Treatment with GLP-1 agonists has been associated with decreased BMI and testosterone and an improved ovulation rate in obese women with PCOS.[33] Increasing evidence shows that weight loss and insulin sensitivity are higher with GLP-1 agonists than with metformin.[34]

- Myoinositol

Myoinositol is an over-the-counter food supplement that increases insulin sensitivity. Compared with placebo, insulin sensitivity in women with PCOS was improved without significantly affecting BMI. [35]

- Bariatric surgery

General population guidelines should be followed when informing about bariatric/metabolic surgery the women with PCOS.

Medications

Clomid citrate (CC) is the primary medication used to induce ovulation in adolescents diagnosed with polycystic ovary syndrome (PCOS)[36]. CC blocks estrogen receptors within the hypothalamus (anti-estrogen). This action results in an increased pulse width of GnRH in the anterior pituitary, leading to elevated FSH production. It is administered for five days, from the 2nd to the 5th day of the menstrual cycle, initiating at 50 mg per day and increasing to 150 mg per day.

Spironolactone, an androgen receptor antagonist, is commonly co-administered with combined oral contraceptives. However, its use requires caution due to the potential for menstrual irregularities and the risk of teratogenic effects, including feminization of male fetuses, if used during pregnancy[37][38]. Alternatives are flutamide, finasteride and cyproterone acetate.

Inositol**,** a non-prescription supplement from the vitamin B complex, can be considered for managing PCOS. It plays a role in various signaling pathways, including those related to FSH and insulin, and may enhance insulin sensitivity. Recent meta-analysis findings indicate that Myo-inositol specifically lowered BMI (mean difference of 0.45 kg/m2) and increased cycle normalization (relative risk 1.79) compared to a placebo, with minimal side effects. However, as a supplement, inositol is not regulated, so it should be used with caution[39].

Vitamin D supplementation, combined with probiotics, showed significant improvements in mental health, hormonal balance, and inflammatory markers in women with PCOS, according to a 12-week randomized trial. The treatment led to reduced T levels, hirsutism, and inflammation, alongside enhanced antioxidant capacity [40][41].

Omega-3 fatty acid supplementation exerts short-term (i.e., 12 weeks) positive impacts on mental health factors, IR, androgen levels, and inflammatory markers, as supported by scientific evidence[42]. Metformin is effective in reducing insulin and androgen levels, while Clomid citrate induces ovulation. Spironolactone, often used with contraceptives, targets hyperandrogenism. Additionally, inositol, vitamin D, and omega-3 fatty acids improve insulin sensitivity, hormonal balance, and mental health.

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