Diagnosing methods and current treatment of Polycystic Ovary Syndrome (PCOS)

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Abstract- PCOS is a diverse endocrine condition with a varied prevalence that affects roughly one in every 15 women throughout the world. Polycystic ovarian syndrome is diagnosed when at least two of the following criteria are met: oligoovulation or anovulation, clinical or biochemical evidence of hyperandrogenism, and polycystic ovary shape. PCOS appears to increase the risk of metabolic disorders, hypertension, and cardiovascular disease in women. The purpose of this paper was to give a review of articles relevant to polycystic ovaries, including pathogenesis, symptoms, diagnosis, and treatment features, as well as its relationship with cardiovascular and arterial hypertension diseases, utilising the databases Pubmed and Scielo.

Keywords- Endocrine, Ovarian Syndrome, GnRH, Hirsutism, Metabolic syndrome

Introduction- PCOS is a diverse endocrine illness characterised by the presence of ovarian cysts, anovulation, and endocrine variation, all of which have a significant impact on a woman's life. The normal menstrual cycle is disrupted when reproductive hormones including LH, FSH, oestrogen, and testosterone are disrupted, resulting in oligomenorrhoea and amenorrhea-like disorders. PCOS is a frustrating condition for women, a difficult condition to manage for clinicians, and a scientific challenge for researchers. [1] As PCOS research progresses, it is critical that study findings be converted into understanding and action among women, healthcare providers, and policymakers. PCOS is the most frequent endocrine disorder among women of reproductive age. According to research conducted in Greece, Spain, and the United States, the prevalence of PCOS ranges from 4% to 8%.[2]
In addition to the fundamental characteristics of PCOS, metabolic and hormonal abnormalities linked with obesity, type 2 diabetes mellitus, and dyslipidemia are frequent. [4] Metabolic syndrome is caused by a combination of these characteristics. The wide range of metabolic abnormalities seen in PCOS may be linked to an increased risk of cardiovascular disease. This could explain why certain women with the condition are predisposed to arterial hypertension. Although the link between changes in arterial blood pressure and PCOS has yet to be fully understood, insulin resistance and hyperandrogenism may explain the higher risk of hypertensive condition, even when age, BMI, and other anthropometric factors are taken into account. [5]

The incidence of PCOS has risen with the use of different diagnostic criteria, and the first community-based prevalence research based on current Rotterdam diagnostic criteria found it to be 18 percent (17.8 ± 2.8 percent). Importantly, in this latest study, 70% of the women were undiagnosed. [3]

There is currently a scarcity of knowledge about PCOS among reproductive-age women in India, particularly in North India. This prospective study was designed to compare socioeconomic status (SDS) and the association of age, body mass index (BMI), education level, and marital status between PCOS and healthy control cases among women in the reproductive age group visiting a tertiary care hospital's department of gynaecology and obstetrics. [6,7]

**Pathophysiology**- Polycystic ovarian syndrome (PCOS) is a chronic condition with no known cause that was initially characterised by Stein and Leventhal in 1935. It's a condition that affects the reproductive, heterogeneous, and metabolic systems. In women of reproductive age, the frequency of the illness ranges from 8.7% to 17.8%. In adolescence, the first clinical signs of PCOS appear. However, there is evidence that the sickness began in the uterus, implying that hereditary factors are involved. [8] Although no obvious pattern of inheritance has been established, several studies have shown a definite role of interleukin-6 and interleukin-10 gene polymorphisms, interferon-γ, and transforming growth factor-beta1 on the development of PCOS. Epigenetic exposures are also causative variables, showing the link between intrauterine exposure and maternal androgens and phenotypes linked to the syndrome. Environmental factors, such as socioeconomic situations and lifestyle, may be linked to ethnic variances in PCOS. [9,10]

The various physiological changes are observed in PCOS that helpful for formation of cyst in a female uterus, are-

1. **Insulin Resistance and Hyperandrogenism**- The actual pathophysiology of PCOS is complicated and poorly understood. Although it is beyond the scope of this study to go into depth, PCOS is caused by a hormonal imbalance caused by a combination of elevated androgens and/or insulin. PCOS is caused by a combination of genetic and environmental factors that cause hormonal imbalances, such as obesity, ovarian dysfunction, and hypothalamus pituitary abnormalities. [11] Excess androgens are caused by hyperinsulinemia, which occurs when insulin mimics the effect of LH and raises GnRH indirectly. [12] Insulin reduces the amount of sex hormone binding globulin (SHBG), a key circulatory protein that regulates testosterone levels. Reduced SHBG causes an increase in free androgens, which causes clinical manifestations such
as hirsutism, alopecia, and acne. Insulin resistance can lead to dyslipidemia, and PCOS individuals are more likely to develop cardiovascular disease and diabetes. [13]

Fig 1, Polycystic Ovary Syndrome (PCOS)

2. **Hyperandrogenism** - Surplus androgens impede normal androgen production, resulting in impaired folliculogenesis. At the early gonadotropin stage, excess androgens encourage the development of primordial follicles and an increase in antral follicles. [14] The release of gonadotropin hormone from the pituitary is triggered by the release of GnRH from the brain. Luteinizing hormone stimulates the LH receptor in ovarian theca cells to enhance androgen synthesis, whereas follicular stimulating hormone activates the FSH receptor in ovarian granulosa cells to convert androgens to estrogens, which encourage follicle development. The dysregulation of the neuroendocrine system is thought to cause an imbalance in the hypothalamic-pituitary-ovarian axis, resulting in an excess of gonadotropin. The increase in GnRH encourages the synthesis of LH rather than FSH, resulting in a significant hormonal increase in LH: In PCOS, the FSH ratio is important. [15,16]
3. **Obesity** - Obesity has been linked to aberrant hypothalamic-pituitary-ovarian axis function, which can contribute to PCOS. Obesity is connected to hyperinsulinemia, which raises lipid levels and causes glucose intolerance in PCOS patients. Obesity stimulates LH, which increases androgen production, resulting in hyperandrogenism. [17] Leptin, an appetite-controlling adipokine, has a direct effect on obese PCOS women's neuroendocrine and reproductive function. Hyperleptinemia can also stifle ovarian follicular development. As a result, reducing visceral fat would regulate hunger, glucose levels, lipolysis, and SHBG, so controlling androgen activity in the ovary.[18]

4. **Obesity** - Obesity has been correlated with abnormal hypothalamic-pituitary-ovarian axis function leading to PCOS development. Obesity is linked to hyperinsulinemia which further increases the lipid profile, glucose intolerance in PCOS patients. Obesity augments the androgen production by stimulating LH, which in turn leads to hyperandrogenism. Leptin, an appetite-controlling adipokine has a direct impact on the neuroendocrine and reproductive function of obese PCOS women.[19] Furthermore, hyperleptinemia may hinder ovarian follicular growth. So, decreasing the visceral fat would control the appetite, glucose levels, lipolysis, and increase the SHBG, thereby regulating the androgen action in the ovary. [20] Furthermore, women with PCOS have increased risk factors for DM2 and CVD, increased impaired glucose tolerance (IGT), DM2 and potentially increased CVD. As obesity rates rise, the public health significance of PCOS will increase. Treatment of obesity through lifestyle intervention is a key treatment strategy in PCOS and improves insulin resistance, reproductive and metabolic features.[21,22]

5. **Genetic Factors** - A few lines of proof propose that the polycystic ovary disorder is heritable. About 3%-35% of moms and 25% of sisters of ladies with PCOS likewise have PCOS, and metabolic disorder predominance is high in their folks and siblings. Accentuated the expanded probability of IR related with specific qualities (like INSIG2 and MC4R) and the specific effect of TCF7L2 SNP on the improvement of type 2 diabetes mellitus (T2DM) and body weight acquire in patients with PCOS (a for every
allele weight acquire of 1.56 kg/m²).[23] Distinguished insulin receptor auto-phosphorylation, diminished degrees of phosphatidylinositol-3-kinase in muscle tissue and instinctive adiposity as plausible instruments. Current comprehension of the pathogenesis of the disorder recommends that it is a complex multigenicjumb. Anyway in uncommon occasions, single-quality changes can lead to the aggregate of the condition.[24]

**Symptoms-** The symptomatic presentation of PCOS usually varies with age, young women mainly complaining of reproductive and psychological problems while older women complaining of metabolic symptoms.[25] Some important symptoms are-

- Missed periods, irregular periods, or very light periods.
- Weight gain, especially around the belly (abdomen)
- Acne or oily skin.
- Ovaries that are large or have many cysts.
- Excess body hair, including the chest, stomach, and back (hirsutism)
- Male-pattern baldness or thinning hair.
- Infertility.

**Diagnosis-** As in the past reviewed, diagnostic standards for PCOS in early life stay controversial, and especially due to the fact the diagnostic pathological facets used in adult women can also be everyday pubertal physiological events. These elements encompass irregular menses, cystic acne, and polycystic ovarian morphology (PCOM).[26] Indeed, it is viable that adolescent hyperandrogenemia is a final result of the lack of full maturation of the hypothalamic-pituitary-ovarian axis all through this time of life. Similarly, prolonged anovulatory cycles are surely ordinary of pubertal improvement alternatively than an early manifestation of PCOS.[27]

As stated above, IR and hyperinsulinemia are often noted in girls with PCOS and may also have an effect on the improvement of PCOS in some patients. However, modern definitions of PCOS do now not consist of obesity, IR, or hyperinsulinemia as diagnostic standards.[28]

According to researchers, the common symptoms of PCOS are hyperandrogenism in adolescents can be clinical or biochemical. Hirsutism is described as excessive, coarse, terminal hairs disbursed in a male fashion, and PCOS is the most frequent motive of hirsutism in adolescence.[29] Hirsutism should be distinguished from hypertrichosis outlined as excessive vellus hair distributed in an exceedingly non-sexual pattern. Delicate hairiness might not be an indication of hyperandrogenemia.[30] Although acne is a common problem in nonage, it is generally flash and may not be reflective of hyperandrogenism. Moderate or severe seditious acne, especially if unresponsive to topical remedy, still, may bear disquisition of androgen excess. [31]

Menstrual irregularities are common until at least 2 years after menarche, therefore irregular menses should not be utilised as the sole criterion for PCOS in adolescence. Menstrual irregularities that last two years in adolescence. Although irregular, post menarche may be an indication of PCOS. Menstruation can last up to a year after menarche without the emergence of PCOS.[32]
1. **Polycystic Ovary on Ultrasound (PCOM):** PCOM is characterized by larger ovaries, thickened stroma, and many tiny peripheral cysts. PCOM is linked to hyperandrogenism, but it isn't necessarily considered a diagnostic feature of PCOS. PCOM is a variable finding in healthy females and adults, although hyperandrogenic adolescents show a higher persistence of PCOM throughout time.[33] The ultrasonographic diagnosis of PCOM in adults via the transvaginal method has been standardized. However, most tests in teenagers are done transabdominally, where the high physiologic follicle number might make follicle count an inaccurate indication for PCOM diagnosis. Because adult diagnostic criteria might lead to an erroneously increased prevalence of PCOM (30–40%), it is critical to utilize proper diagnostic criteria for PCOM in adolescents.[34] The ovary's anatomic appearance varies with ageing. The volume of the ovary grows during adolescence and reaches adult proportions in the years after menarche. It is steady during adolescence and declines beyond the middle of the fourth decade. Follicle size varies with age, with the highest number of tiny follicles occurring throughout adolescence and early adulthood, followed by a dramatic drop in follicle count as one gets older.[35]

2. **Biomarkers:** The ovary's anatomic appearance varies with ageing. The volume of the ovary grows during adolescence and reaches adult proportions in the years after menarche. It is steady during adolescence and declines beyond the middle of the fourth decade. [36]. Follicle size varies with age, with the highest number of tiny follicles occurring throughout adolescence and early adulthood, followed by a dramatic drop in follicle count as one gets older.[37] Except for AMH, there is less evidence on newer biomarkers, and their efficacy in establishing the diagnosis of PCOS in adolescents has yet to be fully validated. The granulosa cells of tiny, developing follicles release AMH, which is a glycoprotein. As already stated Animal studies have suggested that there may be a function for the role of AMH in the development of PCOS. The number of tiny antral follicles (2–5 mm) correlates with AMH serum levels. Adult women can be recognised via transvaginal ultrasonography. AMH levels that have been elevated for a long time have proven a reliable indicator of depression. Detection of hormones in PCOS women.[38] Specific proteins have been identified as indicators for PCOS in proteomic profiling studies. In women with PCOS, Sarray and Almawi, discovered significantly higher sCD40L levels. They hypothesised that sCD40L, a transmembrane glycoprotein that controls numerous cell types in the inflammatory network, may be utilized to predict PCOS in a Bahraini Arab community.[39] Though these findings cannot be applied to other ethnic groups, it is a significant finding that should be replicated and validated in the future. HSP90B1, a stress-inducible chaperone protein linked to cancer cell proliferation, has also been identified as a possible PCOS biomarker. HSP90B1 may contribute to PCOS by boosting granulosa cellular activity in the ovary. To confirm this activity, more research is required. [40]
Treatments- The management of PCOS targets the symptomatology that patients typically gift, organic process, physiological condition, hirsutism, or acne being the foremost common complaints. There are no any approved drugs by FDA/EMA that completely treat the adolescent with PCOS. But some chemical agent and physically exercise are control the symptoms of PCOS.

1. Oral Contraceptive Pills- Oral Contraceptive Pills (OCP) square measure the foremost normally used medications for the long treatment of girls with PCOS and is counselled by the task force and also the Endocrine Society. OCP square measure the foremost normally used medications for the long treatment of girls with PCOS and is counselled by the Task Force and also the Endocrine Society. The oral contraceptive only pills (Progesterone) and in combined form with estrogens. These combinations are commonly useful for the prevention of ovulation and irregular periods.[41,42]

2. Metformine- The metformine is a drug of biguanides class. The metformine is a first line drug for the treatment of cutaneous manifestations and pregnancy complications in women with PCOS. It’s also give synergistic effect with clomiphene citrate.[43]

3. Spironolactone- It is the most potent antiandrogen that has been found to have a demonstrable effect on hirsutism, even when used in conjunction with OCPs. Acne and alopecia have been proven to benefit from it. It's typically well accepted, and its best used with OCP to prevent menstrual irregularities. However, there are no explicit recommendations for the use of spironolactone in the treatment of PCOS in the current guidelines.[44]

4. Aromatase inhibitors - New ovulation-inducing medicines such as anastrozole and letrozole are selective aromatase inhibitors. They're reversible and quite powerful. Unlike CC, which has a half-life of 5–7 days, anastrozole and letrozole only have a 45-hour half-life? Letrozole has received far more research than anastrozole to far. [45] Following the discovery of various side effects of CC, CC's lack of therapeutic efficacy, and the difficulty of gonadotropin therapy, letrozole was presented as an assisted reproduction medication. Letrozole decreases oestrogen synthesis in the hypothalamus–pituitary axis, resulting in higher levels of gonadotropin-releasing hormone (GnRH) and follicle stimulating hormone (FSH).[46]

5. Glucocorticoids- Prednisone and dexamethasone, among other glucocorticoids, have been used to stimulate ovulation. Elnashar et al found that inducing ovulation in CC-resistant PCOS with normal DHEAS by adding dexamethasone (high dosage, short course) to CC is related with no deleterious antiestrogenic impact on the endometrium and increased ovulation and pregnancy rates in a considerable proportion of patients. [47]

6. Gonadotropins- Exogenous hirsutism are a potential second line of treatment for women with PCOS who have shown resistance to CC. 37 Gonadotropins work by inducing ovulation, maintaining and stimulating optimal follicle development by the regulated dose of FSH, and achieving a fertilised follicle. Gonadotropin, unlike CC, does not have a peripheral antiestrogenic action.[48]
Conclusion- In addition to anovulation and infertility, women with PCOS are more likely to develop hypertension and cardiovascular illness as a result of metabolic syndrome. PCOS is diagnosed mostly by clinical examination. Because the origin of PCOS is uncertain, treatment is confined to the management of indications and symptoms. More research is needed to better understand the pathophysiology of PCOS and the development of high blood pressure in women with the condition.

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