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"Polycystic Ovary Syndrome (PCOS)"

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Abstract: *Thepolycysticovarysyndrome(PCOS)is a widespread reproductive disorder that encompasses many associated health conditions and impacts various metabolic processes and alargeproportion of women of reproductive age are suffering from PCOS. It is defined as a syndrome of ovarian dysfunction along with polycystic ovary morphology and hyperandrogenism. It enhances risks of type II diabetes, insulin resistance(IR) and cardiovascular disease. The etiology of the disease remains unclear. Different factors could result in different manifestations and many of these are related to predispositions. Among adolescent patients it is difficult to diagnose PCOS due to overlapping of physiological changes due to puberty and features of PCOS syndrome. Day by day the technology of ultrasonography is improving and precision is increasing, but remains reliant on the specific equipment available.Small antral follicles are precisely seen on ultrasound which synthesize Serum AMH and could help us to diagnose PCOS but there are still many aspects that require elucidation. Currently, there is no exact cure for PCOS but is treated according the symptoms seen. In this mini-review we have attempted to identify some of thesecorrelations.*

Keywords:*Polycystic ovary syndrome; Anti-Müllerian Hormone (AMH) ; Hyperandrogenism*

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I. Introduction

Polycystic Ovarian Syndrome (PCOS) or Hyperandrogenic disorder (HA) is a complex endocrine-metabolic disorder. It was first investigated by Stein and Leventhal .It is one of the most common disorder encountered in women in their reproductive age. It is characterized by menstrual dysfunction and multi-hormonal imbalance, the most prevalent being hyperandrogenism with both short term and long term effects among which infertility is the most alarming consequence. In Indian adolescence prevalence of PCOS is 9.13 percent according to a study conducted by Nidhi, R et al. According to a study conducted in U.S. 11 percent women of reproductive age group are afflicted by PCOS; however in adolescents it may be as high as 50 percent. Around the world, almost 70 percent of the adolescent cases goes undiagnosed due to overlapping of puberty changes and also due to other pathologies such as obesity, ovarian and adrenal neoplasm and adrenal hyperplasia.

PCOS is not only associated with the reproductive life of women but also leads to many other complications. An increased prevalence of several pathological disorders in aging women such as obesity, dyslipidemia, hypertension, metabolic syndrome(MS) and Diabetes Mellitus Type 2 (DM2) are seen in women suffering from PCOS than the women without PCOS. Other alterations such as endothelial dysfunction and chronic low-grade inflammation state which underlies greater risk of developing cardiovascular disorders. Therefore, accurate and early diagnosis of PCOS is necessary to prevent further comorbidities. Obesity is one of the most common sign due to PCOS in world with almost 35 percent women being affected.

PATHOPHYSIOLOGY

Initially it was considered that the main cause of PCOS is excessive intrauterine androgen. However, recent studies shows that neither there is any association between excessive prenatal androgen exposure and the development of the disease in the youth nor an elevation in androgen in the cord blood in females born to PCOS suffering women. No sole cause of PCOS has been determined yet. The most effective theory is that the disorder is a multifactorial disease involving uncontrolled ovarian cycle, aberrant insulin signaling, excessive oxidative stress and environmental/genetic factors.

In PCOS, physiological events in the ovary and folliculogenesis are rendered. High level of Anti-Müllerian Hormone (AMH) or Müllerian-inhibiting hormone is the main cause of disrupted folliculogenesis[7]. AMH is a glycoprotein hormone secreted by granulosa cells and has maximum expression in small antral follicles and exerts inhibition of primordial follicle initiation and follicle sensitivity to follicle-stimulating hormone (FSH). AMH level progressively decreases as follicles increase in size which is mandatory for transition from primordial to primary stage, dominant follicle selection and progression of ovarian cycle. In

women with PCOS, higher level of AMH is seen resulting in long disruptive ovarian cycles. Almost 4 times higher AMH is seen in women with PCOS when compared to normal women.[10]

Hypothalamus-hypophsis-ovary axis (HHOA) disturbance is another feature of PCOS, with increased secretion of Gonadotropin releasing hormone (GnRH) and luteinizing hormone (LH)[12]. High level of this hormones leads to greater androgen synthesis in ovarian theca cells.Feedback sensitivity to both estradiol and progesterone in gonadotropic hypothalamic cells is decreased which is an action induced by hyperandrogenism resulting in increased secretion of GnRH and LH. This is an excellent example of self-perpetuating pathophysiologic cycles in which hyperandrogenemia plays an important role in causing PCOS. The constant growth of follicles and loss in selection of dominant unit leads to hyperstimulation of the follicles. Hence the disorder is referred as 'Polycystic Ovarian Syndrome'[13].

Also, decreased insulin sensitivity attributable to a postreceptor binding defect in the insulin signaling pathways has been identified as an intrinsic component of PCOS, independent of obesity. It was alsoreportedan alteration in gene expression of some players in insulin signaling pathways by microarray gene analysis. Moreover, PCOS has been associated with increased glycooxidative stress secondary to mitochondrial dysfunction. Oxidative stress can itself induce insulin resistance and hyperandrogenism in patients with PCOS.[2]

DIAGNOSIS

Even though insulin resistance and obesity are considered intrinsic to PCOS,however none of them is included in the guidelines and should thereforebeusedfordiagnosticpurposesonly.National Institutes of Health Criteria (NIH) in 1990 defines hyperandrogenism and oligo/amenorrhea anovulation as the criteria for diagnosis of PCOS. Later, in 2003 Rotterdam Criteria included polycystic ovarian morphology on ultrasound as a new criteria that is to be included in the previous two mentioned criteria.

The European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine Rotterdam developed and enlarged the diagnosis of PCOS, requiring two of three features: oligo/amenorrhoa anovulation, clinical and/or biochemical hyperandrogenism and polycystic ovarian morphology (PCOM) visible on ultrasound. Finally, Androgen Excess Society described Hyperandrogenism as the main culprit of PCOS along with ovarian dysfuntion and/or polycystic ovary. AES considers presence of excess androgen is the main cause in development and pathogenesis of PCOS and stated that androgen excess should be present and accompanied by oligo/amenorrhea anovulation or polycystic ovaries or both.

Exclusion of other androgen excess disorders should be excluded such as non-classical congenital adrenal hyperplasia (NC-CAH), Cushing's syndrome, androgen-secreting tumors, hyperprolactinemia, thyroid diseases, drug-induced androgen excess, as well as other causesofoligomenorrheaoranovulation[15].Antral follicle count (AFC) on ultrasound are considered as one of the diagnostic measure in Rotterdam Criteria. Daybydaytechnologyofultra-sonographyadvancesandprecision of ultrasonography devices increases, so the number of small antral follicle also increases in ultrasonography, but are dependent on the specific equipment. Serum AMH is synthesized by small antral follicles, which are quite the ones seen inultrasound.

DIAGNOSIS IN ADOLESCENTS

Held in Amsterdam in 2012, the third PCOS Consensus workshop meeting reported that the diagnosis of PCOS in adolescents should meet the Rotterdam criteria and is hence similar to the diagnostic features in adults. However, diagnostic practices for adolescents with PCOS tend to be inconsistent and variable among endocrinologists and gynecologists. Diagnosis of PCOS in children and adolescence is difficult due to the pubertal physiological changes are almost same and mimics the signs and symptoms of PCOS. The overlap between physiological changes due to puberty and pathological PCOS may leads to misdiagnosis of PCOS leading to unnecessary treatments[24].

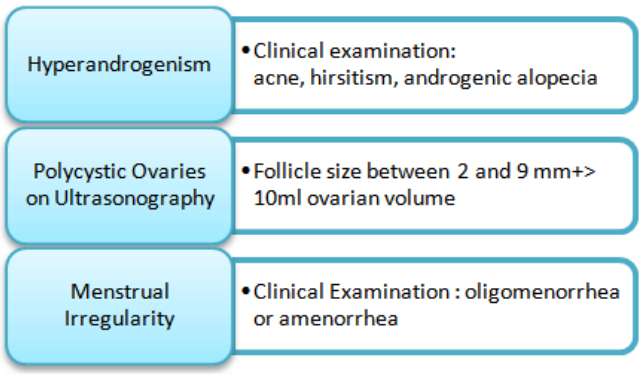

Fig: Signs and symptoms of patients with PCOS

Hyperandrogenism

Puberty is characterized by physiological hyperandrogenism. Studies reveals that during puberty testosterone levels rises and reach peak level within a few years after menarche. This may overlap with the pathological hyperandrogenism and therefore overlaps PCOS[25]. Measurement of testosterone levels does not resolve this uncertainty because testosterone concentrations are highly influenced by the stage of puberty and the menstrual cycle along with other factors. In addition, no cutoff values or reference rangesforandrogenlevelsarewelldefinedinfemaleadolescents. Moreover, acne, which is largely seen during puberty, is not correlated with hyperandrogenism[26].

Polycystic Ovaries on Ultrasonography

During puberty, normal physiological changes and variations in volume and size makes it difficult to diagnose PCOS using ultrasonography[27]. Normal ovarian volume in female adolescents is considered equal to or less than 10 ml for diagnostic purpose.

Menstrual Irregularity

Physiological menstrual irregularities such as oligomenorrhea are frequent during the first 2 years after menarche[19]. It is due to lack of maturation of hypothalamic-hypopituitary-ovarian axis. This may leads to improper diagnosis of PCOS in adolescents, hence it is an unreliable criterion for diagnosis of PCOS[20] . It is suggested to postpone diagnosis for 2 years after menarche to establish normal menstrual cycle. Close observation of menstrual cycles reveal difference between physiological anovulation and pathological PCOS.

CLINICAL FEATURES

PCOS is mainly characterized by hyperandrogenism, ovarian dysfunction and polycystic ovaries. Following are the features of PCOS:

1. Menstrual Irregularities

Physiological menstrual irregularities such as oligomenorrhea are frequently seen in adolescents[19], mostly during the first 2 years after menarche, due to lack of hypothalamic-hypopituitary-ovarian axis[20]. Therefore, menstrual abnormalities are not a reliable criterion for diagnosing PCOS in adolescents. Thorough study and observation is required to differentiate between physiological anovulation due to puberty from pathological anovulation caused due to dysfunction identified in PCOS [21]. Early diagnosis of PCOS is not properly assured due to physiological anovulation.

Based on the survey conducted, it was seen that in almost7.6% women menstrual cycle reoccurs after 2-3 months and in 22.8% of women menstrual cycle changes everytime. The figure shown below describes the reoccurrence of menstrual cycle among women of all ages.

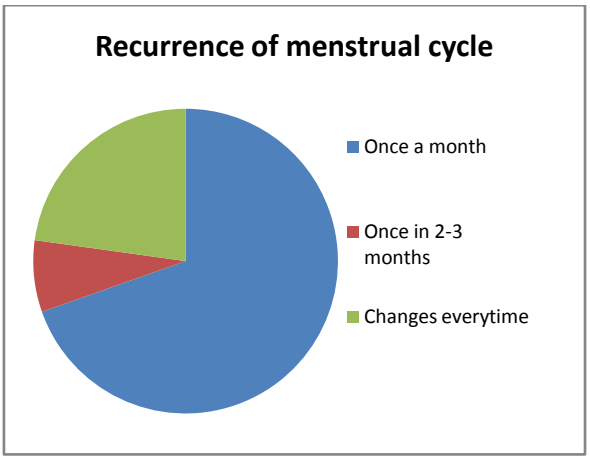

Fig: Recurrence of menstrual cycle

2. Obesity

Obesity is considered one of the most important features of PCOS. Women with PCOS are at higher risks of becoming obese. Many studies reveals increased visceral and subcutaneous body fat distribution due to increased androgen production rates are seen in women with PCOS [17]. This obesity follows a masculinized body fat distribution. Obesity plays a major role in expressing metabolic features of PCOS.

Women with PCOS have higher risks of atherosclerosis, altered vascular endothelium and arterial stiffness. They also have an atherogenic lipid profile associated with elevated levels of low-density lipoprotein, triglycerides and cholesterol, along with decreased levels of high-density lipoprotein [35]. Worsened cardiovascular profile and associated complications are seen in women with PCOS. Obesity by itself is not the main cause of these complications but it accompanies it.Whether obesity is the cause of PCOS or whether PCOS leads to obesity is not still known [36].

3. Onycholysisand Onychorrhexis

Onycholysis- separation of the nail plate from the nail bed due to disruption of the onychocornealband [26] and onychorrhexis- splitting of nails in lengthway bridges are also the possible alterations in PCOS [27].

4. Acne and sebaceous gland

Sebaceous glands are androgen-dependent; also sebocytes are highly sensitive to androgen which is responsible for exacerbation in PCOS which causes acne and seborrhea. Proliferation of sebocyte especially in mid-back, forehead and chin and secretion of sebum, a mixture of lipids including glyceridessqualene free fatty acids (FFA) and cholesterol.Lypolytic enzymes breaks down triglycerides produced in the sebocyte which is caused due to the bacterial infection. The resulting FFA that are released into sebaceous ducts by apocrine glands are responsible for the characteristic odor observed in these patients[30].

5. Hirsutism

Hyperandrogenism causes the excess growth of hair. Normally, in females past pubarchethemajorandrogenicmoleculesaredehydroepiandrosterone sulfate (DHEAS), androstenedione, dehydroepiandrostene- dione, testosterone, and dihydrotestosterone (DHT), in descendingorderofserumconcentration.Onlytestosterone and DHT can bind to the androgen receptor and promote hair follicle changes[31]. Hirsutism is known as the presence of excessiveterminalhairinareasofthebodythatareandrogen- dependent which are usually hairless or with limited hairgrowth, such as the face, chest, areolas, abdomen, and upper thighs.

Althoughhyperandrogenemiaisthetriggerforhirsutism, the rate of hair growth is not proportional to the degree of hyperandrogenism,supportingaparallelroleforandrogen receptor localizationand sensitivity in the development of hair and other skin manifestations, such as acne, seborrhea or alopeciaHirsutism can be assessed through the Ferriman-Gallwey Score [37], which evaluates the presence of terminal hair in the upper lip, chin, chest, upper and lower back, upper and lower abdomen, thighs, andarms.

6. Cardiovascular Disorders

Dahlgren et al. in 1992 identified that women with PCOS have 7 times higher risk of myocardial infarction when compared with women without PCOS [33]. More recent studies suggests that patients with PCOS have significantly elevated levels of circulating biomarkers, including lipoprotein A and C-reactive protein [34].

Androgen Excess-PCOS society in 2010, provided a consensus statement regarding increased risk of

CVD in women suffering from PCOS and developed a guideline to prevent such complications [38]. Even though the increased cardiovascular risk markers and the indubitable presence of CVD risk factors in this population, uncertainty remains regarding the increased cardiovascular morbidity and mortality in patients with PCOS[20]. Discrepancy between studies might be due to the heterogeneous nature of the populations studied. Therefore, supplementary methodologically rigorous trials are needed to determine the absolute risk of CVD in patients with PCOS throughout ageranges.

7. Diabetes Mellitus Type II

PCOS confers a substantially increased risk for type 2 diabetes mellitus and gestational diabetes from early ages. About 1 in 5 women with PCOS will develop type II diabetes [2]making impaired glucose tolerance a common abnormality in this disease .Studies reveals that women suffering with PCOS have higher risks of developing type II diabetes mellitus or impaired glucose intolerance compared to women without PCOS[32]. Furthermore, studies in adult womenwithPCOSrevealsagreaterriskfordevelopingdiabeteslaterinlifeandismainlyduetoanincreasedoccurrenceofobesityandinsulinresistanceamongthesewomen[2].

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TREATMENT

As the actual cause of PCOS is unknown, themanagementofPCOStargetsthesymptomatologyforwhich patients usually present, anovulation, infertility, hirsutism, or acne being the most common complaints. Treatment usually requires the corroboration of an interdisciplinary team that can includeafamilypractitioner,agynecologist,andendocrinologist, a dermatologist, a pediatrician, a psychiatrist, and a psychologist.

The treatment section will mainly focus on two major treatment guidelines: the American Task Force [39]andthePCOSAustralianAllianceGuidelines [40].

Lifestyle Changes

Guidelines recommend exercise therapy and calorie-restricted diet as an important part of the management of obesity in women with PCOS. Lifestyles modifications are considered as the first line of treatment and as a necessary practice along with medication [39, 40].

In women with PCOS, obesity is associated with adverse metabolic and reproductive health outcomes.For instance, female fertility significantly decreases with a BMI >30–32 kg/m^2[41]. Trials have suggested that a body weight decrease of even 5% regulates the menstrual cycle, improves fertility, reduces insulin and testosterone levels, decreases the degree of acne and hirsutism, and benefits psychological wellbeing [42].However, so far, neither a specific diet nor exercise schedule has been shown to be superior to another in the management of PCOS. In addition, it is difficult to ascertain the effectiveness of such interventions based on the limited data which sometimes address specific subgroups of women with PCOS.Further research is required to compare outcomes of different lifestyle management techniques with or without medical therapy for all associated clinical outcomes.

Medical Treatment

Symptomatology, if not resolved by lifestyles changes, medical treatment may be added for better management.

Oral Contraceptive Pills

OCParethemostcommonlyusedmedicationsforthelong-term treatment of women with PCOS and have been recommended by the Task Force and the Endocrine Society [39],theAustralianAlliance[40] andthePCOS Consensus Group as first-line treatment for hyperandrogenism and menstrual cycle irregularities in women withPCOS.

By suppressing the hypothalamo-pituitary-ovarian axis, contraceptive pills reduces LH secretions, enhances sex hormone binding globulins, and decrease free testosterone levels. This resolves hyperandrogenism-mediated symptoms improving acne and hirsutism, corrects menstrualcycleabnormalities,andprovidesameanforeffectivecontraception.A minimum of 6 months of OCP regimen is usually required to obtain satisfactory results against acne and hirsutism [45]. Even though guidelines do notspecifytheuseofoneOCPoveranother [39], the best choice for symptomatic treatment is considered to be low-dose oral contraceptives that contain anti-androgenic or neutral progestins [45].

A number of clinical trials associated the use of OCP in patients with PCOS with increased risk of insulin resistance [39]. Also the concerns about the negative effects of OCP on the cardiovascular profiles of females with PCOS have been raised [44].Nevertheless,datafromrandomized control trials and observational studies demonstrated that OCP are indeed effective and safe for the treatment of patients with PCOS with their benefits outweighing their risks [46].

Clomiphene citrate is considered as the first line of treatment for anovulatory infertility by both the guidelines [39, 40]. Laparoscopic ovarian drilling, *in vitro* fertilizations and exogenous gonandotropins are considered as the second line of treatment [15] if clomiphene citrate, with or without metformin fail to achieve fertility.

II. Conclusion

PCOS was initially described by Stein and Leventhal (1935) [41], since then an extended amount of knowledge has been learned about it. Yet, there are many things to be discoveredincluding its etiology, progression throughout life, spectrum of symptoms, and various morbidities. The pathogenesis of PCOS remains unknown, with unregulated steroidogenesis, insulin resistance, oxidative stress, and genetic factors contributing, possibly from prenatal life, to thedisease.Supplementarystudiesareneededtobridgebetween the various susceptibility factors that might contribute to PCOS.

Current diagnostic guidelines are still vague and may not diagnose patients with less severe non-classic examples. Also, the guidelines are not specific for adolescents as there is overlapping of pubertal changes and symptoms of pathological PCOS.Proper diagnosis is a crucial step to initiate treatment and prevent future illness, further clinical research should update and unify guidelines and also provide an appropriaterationalefordiagnostictoolsthatcandetectallPCOS phenotypes.

Early detection of long-term morbidities through appropriate screening tests constitutes an essential part of the management of this condition. Guidelines strongly suggests lifestyle modifications as a critical part of the management. Oral Contraceptive Pills (OCPs) are the main medication of choice for anovulation and hyperandrogenism; clomiphene citrate is the drug of choice for infertility. Inositol stereoisomers may become the first line drugs for treatment. Hence, studies assessing their effectiveness should be carried on.

Probable areas of further research activity include the analysis of predisposing conditions that increase the risk of PCOS, specifically genetic and environmental factors, such as endocrine disruptors and diet. In addition, defining alterations of steroidogenesis in PCOS needs to be re-examined to quantify ovarian, adrenal and extraglandular contribution, as well as a change in the blood androgen reference values due to the expanding use of mass spectrometry. Recognizingpremenarchal and postmenopausal phenotypes of androgen excess and PCOS would significantly increase our epidemiologic studies of natural history and intervention studies. Regulation of Intraovarian follicle development and mechanisms of follicle arrest and the impact of metabolic abnormalities on these processes, molecular mechanisms by which insulin excess regulates androgen secretion and metabolism and disrupts follicle developmentare other potential issues for investigation. Current information would suggest that androgen alone may not cause follicular arrest but is mandatory for the process and it is likely that non-steroid directed pathways and other inhibitors are implicated in follicular arrest.

In conclusion, we hope this review provides an updated summary that would help in further research for studying the complex nature of PCOS. Future research may find out the missing blocks in our growing knowledge about PCOS and would help the physicians to provide the finest treatment plan and care for the patients.

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