EDITORIAL

An Updated Overview on Poly Cystic Ovarian Syndrome

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BACKGROUND

Poly Cystic Ovarian Syndrome (PCOS) – Stein Leventhal syndrome is one of the most common metabolic/endocrine system disorders in women of reproductive age. Females having PCOS present with a constellation of presentations associated with the androgen excess along with menstrual dysfunction that significantly influences their quality of life. They are at augmented risk of various morbidities, including insulin resistance (leading to type-2 diabetes), obesity, cardiovascular disease (CVD), infertility, cancer, and psychological disorders.

Stein and Leventhal described it, in 1935, as a disorder in which aapproximately 10 cysts of diameter from 2 and 9 mm appear in one or both ovaries with/without increase in ovarian volume exceeding 10 ml[1]. As stated, it was considered as a disorder of women of reproductive age; however, recent evidences suggest it to be a lifelong syndrome, manifesting since prenatal age. Actually, rendering to the Rotterdam criteria, the prevalence of PCOS in youth varies between a minimum of 3% and a maximum of 26%.[2] However, its prevalence in children is still unknown.[3] PCOS costs significantly huge economic burden. Around five billion dollars are annually spent in America for screening and treatment of the disease and its complications e.g. infertility, hirsutism, diabetes mellitus etc. Women with PCOS are two times more likely to be admitted inpatient as compared to normal females.[4] Hence, early and correct diagnosis is essential not only for the prevention of future comorbidities but also to diminish financial burden on the patient and society.

PATHOPHYSIOLOGY

Numerous hypotheses developed to explain the pathophysiology of the disease. Insulin resistance might be contributing to hyperandrogenemia resulting in PCOS.[5] The best theory about the pathophysiology of PCOS explains it as a multidimensional condition involving deviant insulin signalling, wild ovarian steroidogenesis, unwarranted oxidative stress secondary to mitochondrial dysfunction, and environmental/ genetic factors. Oxidative stress can induce insulin resistance and can cause hyperandrogenism. Role of genetics in the aetiology of PCOS is supported by familial aggregation of the disease and identification of genes on PCOS-suspect loci.[6] Furthermore, a polymorphic fibrillin-3 gene associated with PCOS, has been identified in some families carrying the disease.[7] Intrinsic imperfection in theca cells can somewhat elucidate hyperandrogenemia in PCOS patients. This dysregulation disturbs granulosa cells which yield about three to four times higher levels of anti-Mullerian hormone in women with PCOS in contrast to healthy controls.

CLINICAL PRESENTATION AND DIAGNOSIS:

In adults, for the diagnosis of PCOS one can follow one of the three different guidelines as described in the following Figure.

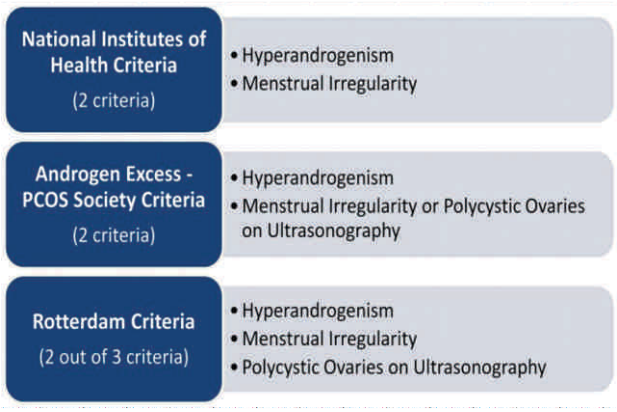

Fig 1: Guidelines for the diagnosis of PCOS.[8]

Although conditions such as obesity and insulin resistance are considered central to PCOS, none is included in the guidelines.[9] Each of the guidelines needs ruling out of any pathological situation that might describe the menstrual irregularity or hyperandrogenism. Additionally, diagnosis in

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adolescent girls is highly arguable.[10] The clinical presentation of PCOS varies with age, young women usually complaining of psychological and reproductive problems whereas older ones complaining of various metabolic symptoms. A detailed history, physical and systemic examination, and investigations should be conducted for appropriate diagnosis. Discontinuation of any hormonal medicines around a month prior to lab testing, along with planning of labs closer to the luteal phase of cycle are recommended for more precise results. Additionally, testing should include measurement of body mass index (BMI), lipid profile, and blood glucose levels. Screening for thyroid status by assessment of thyroid-stimulating hormone levels is important as these are a common cause of menstrual irregularity.

These are some key features:

- Hyperandrogenism present clinically with acne, hirsutism, alopecia, acanthosis nigricans etc. and on investigating high levels of testosterone and androstenedione are found.
- Menstrual irregularity presents as amenorrhea or oligomenorrhoea. Investigation shows high levels of luteinizing hormone.
- Polycystic ovaries on ultrasound shows twelve or more small follicles in one or both ovaries and follicle size is between 2-9 mm with an ovarian volume of 10 ml or more.

ACCOMPANYING INDISPOSITION

Insulin resistance:

Nowadays, insulin resistance is thought to be the core pathogenic factor for amplified metabolic disturbances in patients with PCOS. It explains menstrual irregularity, hyperandrogenism, and other metabolic manifestations of the disease. Hyperinsulinemia is present in 85% of women with PCOS. Increased insulin levels, along with raised luteinizing hormone, trigger the arrest of follicular growth resulting in anovulation. Hyperinsulinemia also disturbs the pulsatility of gonadotropin-releasing hormone (GnRH), decreases the sex hormone-binding globulin (SHBG) and stimulates ovarian androgen production. Lifestyle modifications and insulin-sensitizing drugs improve hyperandrogenism in women with PCOS. When insulin-sensitizing hormone, leptin is used, it decreases androgen levels and helps in regularizing menstruation in affected women. Six months of lifestyle modifications significantly reduced anovulation in affected obese women.[12] This is one of the critical aspect in the treatment of women with PCOS, which results in the contemplation of insulin-sensitizing agents as critical part of the management of the disease. These agents include metformin, thiazolidinedione and myo-inositol supplements.

Type-2 diabetes mellitus:

PCOS deliberates a significantly increased risk for type-2 diabetes mellitus and gestational diabetes. Around 1 in 5 women with PCOS will develop type-2 diabetes making glucose intolerance a common abnormality in this disease.[13]

Obesity:

An established risk factor for PCOS is Childhood obesity. Obesity is one of the most important features of PCOS. Its prevalence in patients with PCOS varies from 60 to 75%. Alternatively, women with PCOS are at a higher risk of developing obesity. Many studies reveal that females with PCOS have increased subcutaneous and visceral body fat distribution because of increased androgen production.[14] PCOS patients have an atherogenic lipid profile. Whether PCOS leads to obesity or whether obesity leads to PCOS is still debatable.[15]

Cardiovascular dysfunction:

Many studies established a burden of complex indicators of atherosclerosis (arterial stiffness, coronary artery calcification and endothelial dysfunction) with relatively early onset cardiovascular dysfunction (CVD) in patients with PCOS. In 2010, the PCOS society provided a consensus statement about increased risk of CVD in women with PCOS and developed a guideline for prevention of such complication. Uncertainty still remains concerning the increased cardiovascular morbidity and mortality in these patients.[16]

Infertility And Complications in Pregnancy:

PCOS is associated with reduced fertility because of associated gynaecologic and endocrine abnormalities that influence ovarian function and quality. A study in 2015 concluded that infertility is ten times more common in women with PCOS in contrast to healthy controls. Some studies suggested that women with PCOS who conceive after treatment usually

suffer from complications of pregnancy e.g. pregnancy induced hypertension, preeclampsia and gestational diabetes to a greater extent as compared to matched controls. Others suggest greater risk of miscarriage in women with PCOS. Women with PCOS are at a 2.5 times higher risk of giving birth to growth restricted babies in comparison to controls.[17]

Cancer:

PCOS women have a three times increased risk of developing endometrial cancer that is usually well differentiated and with good prognosis. This is explained due to the presence of many risk factors in these females which are associated with the development of endometrial cancer such as, insulin resistance, type II diabetes mellitus, obesity, and anovulation. Anovulation causes unopposed estrogen exposure to the uterine endometrium. It can subsequently trigger the endometrial hyperplasia and ultimately leading to endometrial cancer.[18]

Psychological well being:

Associated symptoms of PCOS e.g. obesity, hirsutism, acne and irregular menstrual cycles are major culprits to the psychological stress experienced by the patient due to the her body image and challenging of her female identity. (Women with PCOS are more prone to anxiety, depression, recreational drug use, abnormal eating, and psychosexual dysfunctions in contrast to healthy controls.

MANAGEMENT

Treatment of symptomatology is usually the target for the management of PCOS. The patients usually present with infertility, anovulation, acne, or hirsutism being the most common complaints. Management usually requires the involvement of an multi-disciplinary team that can include gynaecologist, family practitioner, dermatologist, paediatrician, a psychiatrist and endocrinologist.

Lifestyle modifications:

Guidelines recommend calorie-restricted diet and exercise as a central part in the management of PCOS specially the women with obesity. Lifestyle modifications and cost-effective treatment both are essential to management of PCOS.[19]

Medical treatment:

If symptomatology do not resolve by simple lifestyle changes, medical treatment must be added for the management of PCOS patients.

Metformin (Glucophage)

Metformin, a biguanide antidiabetic drug, acts by hindering hepatic glucose production and increasing the peripheral insulin sensitivity. Metformin treatment of PCOS specially of obese women with impaired glucose tolerance proved helpful in improving insulin sensitivity, increasing glucose tolerance, and in decreasing elevated androgen levels. It can also be used in combination with clomiphene citrate to treat subfertility.

Pioglitazone:

The use of pioglitazone was also studied in PCOS patients and data revealed that it results in a decrease in insulin resistance by decreasing fasting serum insulin levels.[20] Oral contraceptive pills (OCP):

Most commonly used medications for the long-term treatment of women with PCOS are the OCPs. The Task Force and the Endocrine Society and the PCOS Consensus Group have also recommended OCPs as first-line treatment for hyperandrogenism and menstrual cycle irregularities in patients with PCOS.

OCP suppress the hypothalamo-pituitary-ovarian axis, which in turn decreases LH secretions, increases sex hormone binding globulins and consequently decreases free testosterone levels. This results in hyperandrogenism-related symptoms e.g. improving acne and hirsutism, revises menstrual cycle abnormalities, and provides effective contraception.[21] A minimum of 6 months of treatment is usually required for satisfactory results in hirsutism and acne. Clomiphene citrate is considered as first line treatment of infertility (anovulatory). Laparoscopic ovarian drilling, exogenous gonadotropins and in-vitro fertilization are second line of management once clomiphene citrate with or without metformin fails.[22] D-chiro-inositol (DCI) and myo-inositol (MYO):Novel treatments of PCOS and are attaining more recognition due to minimal side effects. These are D-chiro-inositol (DCI) and myo-inositol (MYO); two isomers of inositol - insulin-sensitizing molecule. When combined with folic acid, MYO decreased hyperstimulation syndrome in PCOS females undergoing treatment. Another study showed significant improvement in symptoms in terms of

better lipid profile, more menstrual cycle regularity, and less acne, after the use of combination of MYO-DCI.[23]

SCREENING

Appropriate management of the patient needs not only to treat symptoms but also to foresee and to prevent any morbidity that might develop later in life.

These women should be routinely screened for type-II DM. Studies have shown that screening with fasting blood glucose levels alone under-diagnose type-II DM in PCOS patients, missing up to 50% of diabetics. Guidelines recommend screening such women using an oral glucose tolerance test. This screening to be done every 3–5 years in women without risk factors for type II-DM and annually in women with risk factors. Patients with PCOS should be screened routinely for CVD risk factors. Guidelines recommend body weight and BMI measurements, assessment of smoking, monitoring of blood pressure, and a complete lipid profile. Screening of PCOS patients not only for anxiety and depression but also for eating disorders, negative body image, and psychosexual dysfunctions etc. is also recommended.

While concluding, it is important to emphasize that if the physicians want to provide the finest care for these patients, future research work has to find the missing blocks in our increasing information about this syndrome/disease.

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