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Polycystic Ovary Syndrome (PCOS) And Fertility

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Introduction: -

The polycystic ovary syndrome PCOS is conventionally defined as a combination of hyperandrogenism (hirsutism and acne) and anovulation (oligomenorrhea, infertility, and dysfunctional uterine bleeding) with polycystic ovaries. At ultrasound, it is the main gynecological endocrinopathy of reproductive age, affecting 6% - 10% of women in menacme. It is the most common cause of infertility due to anovulation. In many countries, it represents the leading cause of female infertility. The specific pathophysiology of this syndrome has not yet been established, however it is associated with the presence of insulin resistance, obesity, diabetes mellitus type 2, dyslipidemia, metabolic syndrome, hypertension, cardiovascular disease, hyperplasia and endometrial carcinoma. When it is considered in the presence of menstrual disorder, diagnosis of PCOS is obtained in 30% - 40% of patients with primary or secondary amenorrhea and in 80% of patients with oligomenorrhea.[9]

Classification PCOS:

Affects women of childbearing age without higher prevalence by ethnic groups, but the signs and symptoms may differ by ethnicity. Today, the most widely used tool for diagnosing PCOS are still the “Rotterdam Criteria”; its prevalence is up to five times higher than when defined by the NIH criteria. Only a third of patients have the classic form of the syndrome described by Stein and Leventhalin 1935. The concept of PCOS is very broad; it is clinically characterized by the presence of menstrual dysfunction, chronic anovulation and hyperandrogenism. The three main consensuses on PCOS defined the criteria for diagnosis which are highlighted below:

The Rotterdam ESHRE/ASRM—Sponsored PCOS Consensus Workshop Group Fertility and Sterility (2003)

Presence of 2 out of 3 criteria:

1) Oligoovulation or anovulation
2) Clinical or biochemical signs of hyperandrogenism
3) Polycystic ovaries on ultrasound.

As defined by the Rotterdam Criteria in 2003, polycystic ovaries have as their concept, the presence of at least one ovary of 12 or more follicles with diameters of 2 - 9 mm and/or increase the ovarian size > 10 ml (The ESHRE Rotterdam/ASRM, 2004). In addition to these criteria, other medical conditions that can cause chronic anovulation and androgen excess should be excluded, such as:

- Hyperprolactinemia/hyperthyroidism
- Congenital adrenal hyperplasia, classical and nonclassical form
- Cushing’s syndrome; secretory ovarian tumor of adrenal androgens

The Thessaloniki ESHRE/ASRM—Sponsored PCOS (2006)

In 2006, The Androgen Excess and PCOS Society (AE-PCOS) published its positioning regarding the diagnosis of polycystic ovary syndrome. According to this association, the androgen excess needs to be present, either by clinical signs, or by biochemical hyperandrogenism. Thus, for diagnosing of the syndrome, two of the following criteria would be necessary:

1. Oligo and/or anovulation and polycystic ovaries on ultrasound
2. Clinical or laboratory evidence of androgen excess.

To get to these criteria, they considered the syndrome as an androgen excess disorder and its fundamental characteristics: menstrual or ovulatory dysfunction, hyperandrogenemia, clinical hyperandrogenism and polycystic ovary. Further, the association pointed out that, the resulting phenotypes

from the combination of such characteristics, as a group, but not necessarily individually, have insulin resistance and attendant risk of metabolic abnormalities.

The Amsterdam ESHRE/ASRM—Sponsored 3rd PCOS Consensus, 2012

Most recently defined presence of 2 out of 3 criteria:

- Menstrual disfunction and/or polycystic ovary
- Hyperandrogenia and/or hyperandrogenism
- The ultrasound showing a polycystic ovary.[9]

Categories of recommendations in the PCOS guideline

EBR	Evidence-based recommendations are made where evidence is sufficient to inform a recommendation made by the guideline development group
CCR	Clinical consensus recommendations are made in the absence of adequate evidence on PCOS. These are informed by evidence in other populations and are made by the guideline development group, using rigorous and transparent processes.
CPP	Clinical practice points are made where evidence was not sought and are made where important clinical issues arose from discussion of evidence-based or clinical consensus recommendations

Revised diagnostic criteria of polycystic ovary syndrome

1. Chronic anovulation
2. Clinical and/or biochemical signs of hyperandrogenism and exclusion of other etiologies.

Revised 2003 criteria (2 out of 3)

1. Oligo- or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries[5]

Hyperandrogenism

Clinical phenotyping of PCOS involves determining the presence of clinical and/or biochemical androgen excess (hyperandrogenism), while excluding related disorders.

Clinical Hyperandrogenism: Most participants felt that the primary clinical indicator of androgen excess is the presence of hirsutism. However, the following issues should be emphasized:

- Normative data in large populations are still lacking.
- The assessment of hirsutism is relatively subjective.
- Few physicians in clinical practice actually use standardized scoring methods.
- Hirsutism is often treated well before the patient is ever evaluated endocrinologically.
- Hirsutism may be significantly less prevalent in hyperandrogenic women of East Asian origin or in adolescence.[4]

Subfertility and pregnancy complications

Insulin resistance and type 2 diabetes

PCOS is associated with insulin resistance and hyperinsulinemia. Women with PCOS had increased prevalence of impaired glucose tolerance and DM2 independently of BMI. In a Danish registry study, the risk of DM2 was 4 times greater among women with PCOS. Furthermore, DM2 was diagnosed 4years earlier in women with PCOS compared with unaffected control women. PCOS is associated with impaired glucose tolerance in up to 30% and DM2 in up to 10% of women with PCOS. A 10-year follow-up study found that the age-standardized prevalence of DM2 in women with PCOS in their 40s or 50s is 40%, that is, 6.8 times higher than that of the general female population of a similar age.The prevalence of DM2 in PCOS continues to increase during the late reproductive years. Glycemic status should be assessed (using an oral glucose tolerance test [OGTT], fasting plasma glucose, or HbA1c) at baseline in all women with PCOS and should be repeated every 1–3years depending on other individual risk factors for diabetes present.[3]

Adipokines

The increased incidence and severity of cardiovascular risk factors and of metabolic disturbances in PCOS may be in part related to the abnormal production and release of adipokines and inflammatory factors by adipose tissue. Although traditionally regarded as a storage organ, emerging evidence also strongly suggests that adipose tissue is an endocrine organ, whose altered function may produce widespread cardiometabolic disturbances in PCOS. It is believed that dysregulated adipocyte function and obesity play a pathophysiological role in PCOS.[2]

Metabolic syndrome

Several studies have observed a higher prevalence of Met's in older women with presumed PCOS diagnosis compared with control women. Some of these studies also showed a higher prevalence of Met's in the hyperandrogenic PCOS phenotype compared with the nonhyperandrogenic phenotype. Women with presumed PCOS who did not have Met's at baseline had higher rates of Met's during follow-up of 12years (incidence rates: PCOS: 3.57 versus control: 2.26). This difference was not significant after adjustment for confounders, including BMI, suggesting that women with PCOS who have not developed Met's in their premenopausal years may represent a lower-risk group[4].

Obesity and dyslipidemia

The close relation between elevated BMI levels and PCOS is obvious considering the fact that PCOS is associated with overweight and obesity (33–88%). However, whether obese patients are predisposed to PCOS or whether they are obese because of their PCOS status is continuously debated. Current evidence suggests that obesity is a modifying rather than a causal factor for PCOS. Indeed, it has been shown that the incidence of PCOS among different BMI groups was quite similar. Hence, it seems that obesity aggravates the reproductive and metabolic phenotype of PCOS.

Obesity increases insulin resistance and the resulting hyperinsulinemia, which in turn increases adipogenesis and decreases lipolysis. Obesity also sensitizes thecal cells to luteinizing hormone (LH) stimulation, resulting in functional ovarian hyperandrogenism. Moreover, obesity affects inflammatory adipokines, which, in turn, increases insulin resistance and adipogenesis. Lifestyle intervention, preferably including diet, exercise, and behavioral strategies, should be recommended in overweight or obese women with PCOS to effectively reduce weight, central obesity, and insulin resistance. Appropriate first-line treatment for patients with PCOS during their reproductive age is lifestyle modification.[3]

Clinical Manifestations

Dermatological clinical manifestations of hyperandrogenism include: hirsutism, acne, seborrhea, alopecia and, in severe cases, signs of virilization. There is considerable heterogeneity in the clinical practice, as well as can be variation in the same patient over time. Moreover, hyperandrogenism cannot define peripheral manifestations as observed mainly in Asian women.

Risk factors and preventive measures

Genetics:-

If a close family member, such as a sister or mother, has the condition, you have an increased, but not guaranteed, chance of developing PCOS. Even without a family history of PCOS, there are other risk factors that can lead to its development.

Diet:-

Additionally, diet has been found to be a contributing factor for PCOS. Fats and proteins from one's diet can form advanced glycation end products (AGEs) when exposed to sugar in the bloodstream.39 These compounds are known to contribute to increased bodily stress and inflammation, which have been linked to diabetes and cardiovascular disease.40 PCOS patients already have an increased likelihood for metabolic syndrome, cardiovascular issues, and diabetes. Thus, it's best to limit exposure to AGEs. Animal-derived foods that are high in fat and protein are generally AGE-rich and prone to more AGE formation during cooking. In contrast, foods that are low on the glycemic index—such as vegetables, fruits, whole grains, and milk—contain relatively few AGEs, even after cooking.

Lifestyle:-

Everyday habits greatly affect the development and severity of PCOS.

- Obesity is widely recognized as aggravating PCOS, so managing a healthy weight, especially abdominal circumference, is recommended.
- Exercise helps to reduce many PCOS symptoms, such as depression, inflammation, and excess weight. Aim to incorporate exercise into your lifestyle. The Centers for Disease Control and Prevention (CDC) recommends 150 minutes (2 hours and 30 minutes) of moderate-intensity exercise per week or 75 minutes of high-intensity exercise per week and incorporating strength training 2 days per week.
- In addition to exercise, increase daily activity by taking the stairs, going on short walks, and stretching throughout the day. No matter the movement, stay consistent and choose an enjoyable activity.

- Women may want to limit inflammatory foods—such as dairy products, foods with gluten, and foods high in glycemic load, such as potatoes, white bread, and sugary desserts—as much as possible. But if those foods do not cause bodily aggravation, then there is no need to eliminate them completely.

Environmental exposure risks:-

Environmental exposures to endocrine-disrupting chemicals may lead to female reproductive health issues, including PCOS. Research shows that endocrine-disrupting chemicals may pose the greatest risk during prenatal and early postnatal development, when organ systems are developing. Endocrine disrupting chemicals can be found in many of the everyday products we use, including some plastic bottles and containers, liners of metal food cans, detergents, flame retardants, food, toys, cosmetics, and pesticides. Limiting personal exposure to endocrine-disrupting chemicals may benefit reproductive health.[8]

Polycystic Ovary Syndrome PCOS and Fertility

PCOS is characterized by anovulation due to a developmental defect of follicles beyond 10 mm in size. The clinical manifestations, including infertility, are related to the hypersecretion of LH (70%) present in women with hyperandrogenism anovulatory women, (the ratio of LH/FSH ratio and high increase in ovarian androgen production). Most of the cycles are anovulatory, making it essential to induce ovulation. Infertility has been considered by the World Health Organization (WHO) as a public health problem.

One of the central goals of the UN Conference Programme of Action on Population and Development in 2015 was to guarantee, for all individuals, access to quality reproductive health services. The agency defined infertility as the absence of pregnancy after two years of regular intercourse, without using any contraception method. However, there is a consensus that, after one year, a process of assessment of possible factors involved should begin. The ESHRE/ASRM recommends that, before startig any intervention, acounseling before conception should emphasize the importance of lifestyle changes, especially weight loss and regular exercises in overweight patients, smoking cessation, and reducing alcohol consumption.

Regarding ovulation inducing drugs, all are associated with the increase in multiple pregnancies, obstetric and neonatal risks. Among the most commonly found female's causes of infertility, it is possible to observe structural changes, ovulatory changes, immune disorders and endometriosis. Infertility patterns may be influencedby many factors, such as the woman's age, frequency in sexual activity, woman's weight and smoking, among others. This way, different techniques should be used to reach an accurate diagnosis.

About 50% of infertile women have also obesity. There is a clear association between obesity and menstrual irregularities, since the adipose tissue is the largest peripheral area for the aromatization of androgens to estrogens, contributing to estrogen production. Women with PCOS have a greater risk of anovulation and infertility. The progesterone dosage may be useful as an additional screening test. Itis also recommendedto exclude other infertility causes besides anovulation, in couples in which the woman has PCOS. The diagnosis of PCOS is very important, because it identifies the metabolic risks, the potential cardiovascular risk and mainly because such a diagnosis interferes directly with the fertility status of these patients.[9]

Discussion and Conclusion

PCOS is recognized as the most common gynecological endocrinopathy, affecting 5% - 10% of women childbearing age. It is also the most common cause of anovulatory infertility. However, there are some difficulties in its diagnosis due to different proposed diagnostic criteria. This is a very heterogeneous syndrome, both in terms of clinical presentation and laboratory manifestations. Women with PCOS have been presented a greater risk of endometrial cancer, which is related to the estrone increase and the high prevalence of anovulatory cycles which favor the endometrial hyperplasia, as it is already known. The overweight is also linked to this type of cancer and represents, therefore, an additional risk factor for endometrial cancer in these patients. Researches also reported the obesity role in the occurrence of PCOS and its infertility relation. A recent study found that obesity by itself was associated with the reduction of ovulatory rates, increasing in the abortion numbers of late pregnancy complications, and perhaps, therefore, increasing the infertility risk which was inherent to the syndrome. Anxiety, depression, stress and personal dissatisfaction, frequently reported by women who live with PCOS may be aggravated by the image body change for consequence of weight gain. PCOS should be diagnosed and treated already in adolescence due to reproductive, metabolic and oncological complications that probably are associated with it. The best way of prevention is through leading an adequate diet and a healthy lifestyle.[9]