

Polycystic Ovarian Syndrome: Pathophysiology and Infertility

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is recognized as the commonest endocrinopathy of women in the reproductive age. The definition, heterogeneity of clinical presentation, variability of symptoms in different age groups, overlapping instrumental and laboratory diagnostic criteria with physiological situations and the etiological hypotheses of PCOS are continuously evolving to accommodate expanding knowledge on the syndrome, which is now known to be more complex than purely a reproductive disorder. This article reviews the pathophysiology aspects known to underlie the ovarian and metabolic abnormalities characterizing PCOS. The interdependence between reproductive and metabolic aspects of PCOS and therapeutic implications for the management of PCOS are also discussed.

Materials and methods: Extensive review of literature of articles published in English language was conducted using the following engines: Google, Yahoo, Medline, PubMed and Medscape.

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INTRODUCTION

The polycystic ovary syndrome (PCOS) is the most frequent pathology among women of reproductive age. It was described for the first time by Stein and Leventhal in 1935.¹ There is still no international consensus on its definition.

The difficulties in finding an agreement on the criteria for establishing the diagnosis of PCOS are related to the intrinsic characteristics of the syndrome: heterogeneity of clinical presentation, variability of symptoms in different age groups, overlapping instrumental and laboratory diagnostic criteria with physiological situations and therefore lack cut-off shared and useful in clinical practice.

The definition of PCOS remains dynamic and controversial subject of debate for many scientific forums. In the

publication of Stein and Leventhal in 1935, it was described for the first time the phenotype of seven cases of PCOS in women with oligo/amenorrhea, hirsutism, obesity and polycystic ovaries bilaterally.¹

In 2003 in Rotterdam ESHRE (European Society of Human Reproduction and Embryology)/ASRM (American Society of Reproductive Medicine). The PCOS consensus workshop group has proposed a revision of the diagnostic criteria, defining PCOS as the presence of at least two of the following criteria together with the exclusion of other etiologies (congenital adrenal hyperplasia, hyperprolactinemia, thyroid dysfunction, androgen-secreting tumors and Cushing syndrome):²

- Oligoanovulation
- Hyperandrogenism (clinical or biochemical)
- Polycystic ovary (morphological sign found at the ultrasound examination)

The sonographic appearance of the ovaries is as defined prevalent in Europe at present, an essential criterion. However, there is still no agreement in the definition ultrasound of polycystic ovaries (PCO) (Fig. 1).

The classic sonographic criteria of Adams include the presence of at least 10 follicles with a diameter of 2 to 10 mm around a hyperechogenic stroma.^{4,5}

Transvaginal ultrasound is the most widely used technique for the ultrasound assessment of PCO. The sonographic criteria have been subsequently modified and, therefore, the increase in ovarian volume ($>10\text{ cm}^3$) and the presence of >12 follicles with a diameter of 2 to 9 mm at least in one ovary.⁶ Must be excluded from this rule women who use oral contraceptive as it transforms the ovarian morphology in healthy women and probably also in women with PCO.²

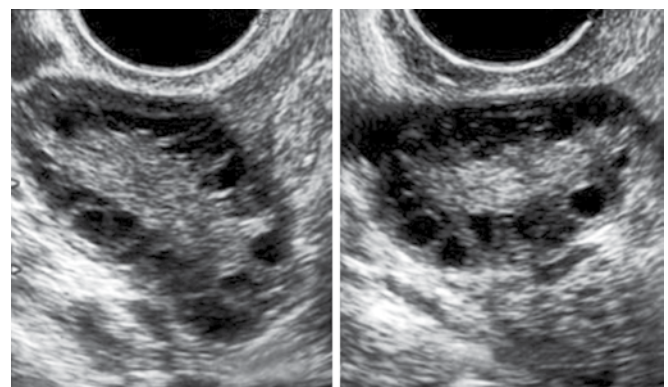


Fig. 1: Ultrasound imaging of polycystic ovaries⁶

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The prevalence of PCO is dependent on the age of the women, 21.6% in women <35 years of age and in women >35 years is 7.9%.⁷

The presence of PCO on ultrasound may be an isolated finding in asymptomatic patients, as well as patients with the typical clinical and biochemical manifestations of PCOS who have morphologically normal ovaries. Currently there is little data in the literature regarding ultrasound (US) parameters in women with PCO and PCOS. This is the subject of scientific debate for the interpretation of the pathophysiology of PCOS which is the base for future investigation and research.

The variability of the description of the ultrasound ovarian morphology (number and location of follicles, hyperechoic stroma) is a fact although recent studies regarding the increase of the volume ovarian (>10 cm³) as the most reliable of ultrasound evaluation of PCOS.⁸

Other authors emphasize the rising importance of ovarian stroma or the relationship between ovarian stroma/total area.⁹ Characteristic the increase in vascularity of the ovarian stroma using the echo-Doppler^{11,12} which in turn can be related to changes in ovarian steroidogenesis in women with PCOS. It is believed that the vascular endothelial growth factor (VEGF) plays an important role associated with an increased stromal flow in patients with PCOS.¹³

CLINICAL PRESENTATION

Menstrual Irregularities

In most cases, menstrual irregularities in women with PCOS begin at menarche and consist of oligomenorrhea or amenorrhea less frequently. In the fourth decade of life more than 70% of women with PCOS spontaneously reaches the menstrual regularity.³⁴ The amenorrhea and oligomenorrhea are consequence of the chronic state of anovulation present in these patients. The anovulation in women with PCOS is related to the coexistence of endocrine and paracrine alterations. It has been documented an increased pulse frequency for the luteinizing hormone (LH).³⁵ The increased pulse frequency of the hypothalamic GnRH promotes the transcription of the beta subunit of LH compared to the beta subunit of follicle-stimulating hormone (FSH).³⁶ It is not clear whether this increased pulse frequency is due to an abnormality of the intrinsic GnRH pulse generator or caused by low levels of progesterone due to the chronic state of anovulation as the progesterone slows the GnRH pulse generator.³⁷ Increased concentration of intrafollicular androgens act in a paracrine manner.

The majority of women with this syndrome have oligomenorrhea interspaced with episodes of irregular vaginal bleeding. The cause of such menstrual like bleeding is not

always report an occurrence of ovulation but can be caused by a sharp fall in plasma levels of estrogen.

Obesity

It is present in 30 to 60% of PCOS patients with body mass index (BMI) greater than 30. However, even in this case the choice of the cut-off can be discussed and amended on the basis of geographical and socioeconomic considerations. The visceral obesity with the increase in the WHR (waist-hip ratio) corresponding to the waist-hip ratio (normal range, 0.82-0.85) is frequent in obese women with PCOS.²²

The presence of obesity in women with PCOS determines a deterioration in the clinical picture from both metabolic and reproductive points of view.²³

Obese women with PCOS compared to normal weight women with PCOS have increased prevalence of glucose intolerance and diabetes mellitus type II,²⁴ higher prevalence of hirsutism,²⁵ increased risk of metabolic syndrome and risk of cardiovascular disease²⁶ as high level of PAI-1 (plasminogen activator inhibitor-1) found in PCOS patients may contribute to increased cardiovascular risk.²⁷ Obesity increases the prevalence of obstructive sleep apnea in patients with PCOS.²⁸

In a recent study, it has been identified a dysregulation of lipolysis in PCOS patients,²⁹ because an increased lipolysis of visceral fat with a consequent increase of free fatty acids released directly into the portal circulation. The levels of free fatty acids in portal circulation are the major modulators of hepatic gluconeogenesis.³⁰ This increased lipolysis at the level of visceral fat may be one of the mechanisms for the increased risk of glucose intolerance.³¹

In obese women with PCOS, exercise, a low-calorie diet and the reduction of body fat lead to an improvement of ovarian function with possible restoration of spontaneous ovulation and reduced risk of type 2 diabetes mellitus.³² Exercise and weight control are certainly to be recommended in view of their strong impact not only on metabolic panel, but also on ovarian function and fertility restoration.³³ If lifestyle measures are unsuccessful, then consider referral to a fertility specialist. Referral should be initiated early for women aged more than 35 years and in couples with additional factors contributing to infertility.

The success for the treatment of obesity requires a multidisciplinary approach involving the dietitian, psychological support and a gynecologist.

Growing evidence that PCOS is a disorder characterized by insulin resistance and hyperinsulinemia.

Insulin resistance is a condition in which a normal concentration of insulin produces attenuated biological effects in cases where the pancreatic function is intact, this involves a compensatory hyperinsulinemia. The presence of insulin

resistance does not imply a systematic glucose intolerance and blood glucose can be normal.

Prospective and retrospective observational studies show that at least 40% of women with PCOS has a glucose intolerance and that in 10 to 20% will develop in middle age (55-65 years) diabetes mellitus type II.^{14,15}

Before the development of frank glucose intolerance, the defect in insulin action can remain latent and only in circumstances which increase insulin resistance may arise, for example, the occurrence of gestational diabetes or glucose intolerance in the case of treatment with corticosteroids.

The molecular mechanism responsible for insulin resistance in PCOS appears to be unique and specific to this syndrome and other than that present in obesity. The most likely mechanism would be an altered phosphorylation of the insulin receptor, resulting in a defect in signal transduction.¹⁶

In women with PCOS ovarian tissue remains sensitive to insulin, although there is a systemic resistance to the action of insulin hormone. Ovarian stimulation seems to involve a system of signal transduction different from that for the transport of glucose, in particular, a different second messenger, probably inositol phosphoglycan.^{17,18}

Insulin and IGF-1 (insulin growth factor-1) are important regulators of ovarian function and influence directly and indirectly ovarian steroidogenesis and androgenic status. Insulin acts directly on theca cells by activating the cytochrome P450c17 with activity 17-alpha-hydroxylase and 17,20-lyase (key enzyme in androgen synthesis) and also enhances the synthesis of androgen synergistically induced by the hormone LH.

Insulin also acts indirectly by suppressing the circulating levels of sex hormone binding globulin (SHBG), resulting in increased free testosterone, the bioavailable fraction of the hormone to the tissues.²⁰

Finally, insulin can suppress the hepatic synthesis of IGF-binding protein-1 (IGFBP-1), thus increasing the bioavailability of IGF-1, an important regulator of the synthesis of ovarian androgens. It also seems possible that the insulin may act at the level of the hypothalamus by modifying the pulsatile secretion of LH, influencing in this way also ovarian steroidogenesis.^{19,20}

Currently, there is no screening test for insulin resistance, while it has been established a criterion for the definition of the metabolic syndrome associated with the syndrome of insulin resistance that includes the visceral obesity, hypertension, fasting hyperglycemia and dyslipidemia (Fig. 2).²¹

Hirsutism

It is a clinical sign of hyperandrogenism. The perception of the presence of hirsutism as a problem depends on cultural and ethnic factors. Commonly used the score Ferriman-Gallwey

for clinical assessment and a score greater than 8 is considered diagnostic.³⁸ The fact remains that an assessment is extremely subjective.

The incidence of hirsutism in Caucasian women is 60 to 70%, while in Japanese women is 30%.³⁹

In PCOS patients, moreover, hyperinsulinism contributes to an increase in the secretion of adrenal androgens in part by increasing the sensitivity to the hormone ACTH.⁴⁰

Acne

A sustained polymorphic dermatosis by a chronic inflammation of the hair follicle. The clinical presentation of the acne includes four pathological events: hyperkeratosis of the follicular canal, the sebaceous hypersecretion, bacterial proliferation and inflammation.

Chronic hyperandrogenism causes an increase in sebum secretion thus forming a collection of fat resulting in overlapping bacterial infection.

It is estimated that roughly one-third of PCOS patients have acne,⁴¹ while the majority of women with severe acne have PCOS.⁴²

Acanthosis Nigricans

It is a mucocutaneous lesion with areas of hyperpigmentation and dark brown color with skin thickening. It is a cutaneous marker of a heightened insulin-resistance and can be present in up to 5% in women with PCOS.⁴¹

Infertility

The main cause of infertility in women with PCOS is due to chronic anovulation. However, it was reported a higher

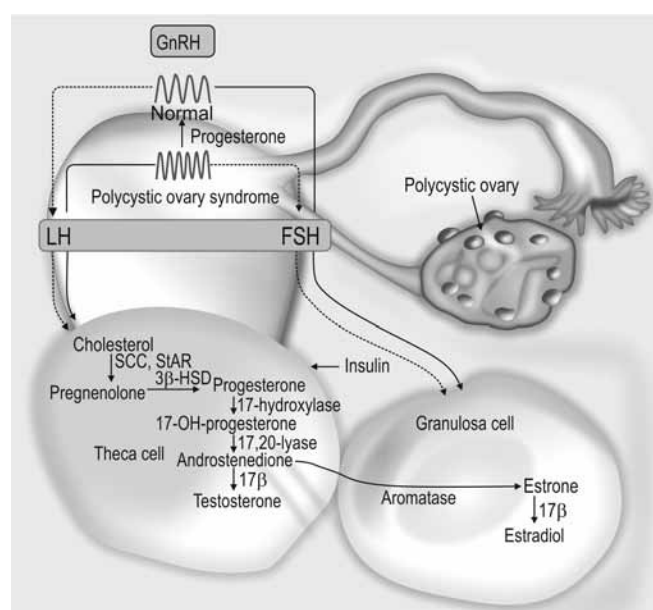


Fig. 2: The hypothalamic-pituitary-ovarian axis and the role of insulin (Courtesy: Ehrmann DA. Polycystic ovary syndrome. N Engl J Med 2005;352:1223-1236)

incidence of polycystic appearance of the ovary (PCO) on US in patients with normo-ovulatory but subfertile⁴³ and repeated pregnancy loss.⁴⁴

The subfertility may be related to the increase in plasma levels of the LH in the follicular phase of the cycle that causes a resumption of the second meiotic division of the oocyte and the premature release of the oocyte.⁴⁵

The mechanism linking PCOS and miscarriage is not yet well known; however, various factors involved in the process of steroidogenesis, folliculogenesis, oocyte maturation and reduced endometrial receptivity contribute to this vicious cycle between PCOS and miscarriage.⁴⁶

The presence of chronic anovulation and high levels of estrogen that persists over the years may lead to an increased risk of endometrial hyperplasia and endometrial cancer.

It is highlighted an increased incidence of endometrial hyperplasia and endometrial cancer in women with PCOS.

In women with PCOS may be present obesity and diabetes mellitus type II, two conditions also associated with increased risk of endometrial cancer.

Therapeutic Implications and Management of Infertility

If pharmacological treatment is required, the best first line treatment is clomiphene citrate, which has a pregnancy rate of 30 to 50% after six ovulatory cycles, although in women with a BMI <30 to 32 kg/m², metformin may have a similar efficacy to clomiphene citrate.^{3,10}

If clomiphene citrate, metformin or a combination of the two is unsuccessful in achieving pregnancy then gonadotropins are the next pharmacological options.³

Laparoscopy with ovarian drilling (LOS) is a suitable second line treatment, if clomiphene citrate with metformin has failed. The pregnancy rate with LOS is as effective as three to six cycles of gonadotropin ovulation induction.³ If all of the above are unsuccessful or if there are other factors contributing to infertility, such as endometriosis or male factors, *in vitro* fertilization (IVF) or intracytoplasmic sperm injection is recommended.

CONCLUSION

The natural history of polycystic ovary and the role of extraovarian factors, such as obesity, insulin resistance and environmental factors in the phenotypic manifestations of PCOS are the subject of scientific debate.

The sonographic appearance of PCO even if found in isolation requires greater attention in its clinical evaluation.

The evolution of polycystic ovaries toward a phenotype of PCOS is still not well coded. The pathogenesis of PCOS and its natural history are the determining factors for a real

assessment of the incidence in patients referred to the infertility clinic.

However, longitudinal studies are needed to clarify the pathophysiology of PCOS and its impact on reproductive health.

The metabolic alterations present in women with PCOS, therefore, require a change in the clinical approach to this syndrome, recognizing that this condition is chronic and with possible long-term consequences.

There are still controversies about the advisability of screening to identify a possible impaired glucose tolerance and insulin resistance in all women with PCOS.

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