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Polycystic Ovary Syndrome, Pathophysiology, and Reproductive Health Implications

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. The clinical picture characterized by both endocrine disorders (hyperandrogenism, menstrual cycle disorders, obesity) and metabolic alteration with implications for women's health and reproductive and metabolic consequences. Leventhal described for the first time a syndrome characterized by polycystic ovaries associated with menstrual cycle disorders, hirsutism, and obesity. The pathophysiology and other metabolic disorders that make the PCOS more complex than originally described are the most common cause of infertility linked to chronic anovulation. In fact, this is a multifactorial disorder that involves the hypothalamus, pituitary, ovary, adrenal, and peripheral adipose tissues, which are simultaneously involved in the pathogenesis of the syndrome.

Keywords: infertility, polycystic ovary (PCO), polycystic ovarian syndrome (PCOS), menstrual irregularities, acne, hirsutism, anovulation, obesity, hyperandrogenism, insulin resistance and hyperinsulinemia, metformin

1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder among women of reproductive age. It was described for the first time by Stein and Leventhal in 1935 [1].

The PCOS Consensus Workshop Group has proposed a review of diagnostic criteria, defining PCOS as the presence of at least two of the following criteria together [2]:

- Oligo-anovulation
- Hyperandrogenism with clinical or biochemical signs
- Polycystic ovary appearance on ultrasound examination

In order to establish the diagnosis of PCOS, it is important to exclude other disorders with a similar clinical presentation, such as congenital adrenal hyperplasia, Cushing's syndrome, and androgen-secreting tumors.

2. Clinical presentation and clinical components in polycystic ovary syndrome (PCOS)

2.1. Menstrual irregularities in women with polycystic ovary syndrome (PCOS)

This often occurs during the adolescent period at the menarche with menstrual irregularities mainly oligomenorrhea or less frequently amenorrhea. Over 70% of women with PCOS spontaneously reach menstrual regularity in the fourth decade of their life with metabolic dysfunction mainly in perimenopausal age [3]. The chronic state of anovulation present in these patients will produce amenorrhea and oligomenorrhea. An elevated pulse frequency for the luteinizing hormone (LH) has been documented [4]. The increased pulse frequency of the hypothalamic gonadotropin-releasing hormone (GnRH) promotes the transcription of the LH beta-subunit compared to the follicle-stimulating hormone (FSH) beta-subunit [5]. It is unclear whether this increase in pulse frequency is due to an inherent anomaly of the GnRH pulse generator or caused by low progesterone levels due to the chronic state of anovulation as progesterone slows down the GnRH pulse generator [6].

Most women with this syndrome exhibit oligomenorrhea with irregular vaginal bleeding episodes. The cause of such bleeding is not always referred to ovulation but may be caused by a sudden drop in plasma estrogen levels [7].

Increased ovarian androgen biosynthesis in the polycystic ovary syndrome results from abnormalities at all levels of the hypothalamic-pituitary-ovarian axis [8]. The etiopathogenesis of PCOs is multifactorial; all these factors act by creating a vicious circle that eventually leads to the syndrome. It is not yet clear at present what pathogenic event that triggers the chain reaction that leads to hyperandrogenism. The clinical manifestation of PCOs is the result of a series of alterations of physiological mechanisms, so there is not always a full expression of this syndrome. PCOs usually occur in puberty with menstrual disorders, hirsutism, and obesity. Alongside endocrine disorders, there are also metabolic disorders which, however, become more and more evident with the progress of time until they become predominant after menopause.

3. Obesity

Obesity is present in 30–60% of patients with PCOS with body mass index (BMI) greater than 30 kg/m² and is often associated with a state of hyperinsulinism. However, even in this case,

the cutoff choice can be discussed and modified on the basis of geographical and socioeconomic considerations. The presence of obesity in women with PCOS results in worsening in the metabolic and reproductive outcomes [9].

Obese women with PCOS compared to women with normal weight with PCOS have increased prevalence of glucose intolerance and type 2 diabetes mellitus [10], higher prevalence of hirsutism [11], greater risk of metabolic syndrome, and therefore cardiovascular disease [12, 13]. Obesity increases the prevalence of obstructive sleep apnea in patients with PCOS [14].

A lipolysis dysregulation in PCOS patients has been documented [15], as an increased lipolysis of visceral fat resulting in an increase in free fatty acids released directly into the portal circulation. The free fatty acid levels in the hepatic portal circulation are the major modulators of hepatic gluconeogenesis [16]. This increased visceral fat lipolysis may be one of the mechanisms for increased risk of glucose intolerance [17].

In obese women with PCOS, physical activity and low-calorie diet intake lead to an improvement in ovarian function and reduction of the risk of type 2 diabetes mellitus [18]. Exercise and weight control are highly recommended because of their direct effect not only on the metabolic framework but also on ovarian function and restoration of fertility [19]. Success in treating obesity requires a multidisciplinary approach involving the dietician, the psychologist, and the physician.

4. Hirsutism

The perception of hirsutism as a problem depends on cultural and ethnic factors. The commonly used Ferriman-Gallwey score for clinical evaluation and score above 8 is considered diagnostic [20]. The fact remains that it is an extremely subjective assessment.

The incidence of hirsutism in Caucasian women is 60–70%, while in Japanese women is 30% [21].

In PCOS patients, hyperinsulinism also contributes to increased adrenal androgen secretion in part by increasing adrenal sensitivity to adrenocorticotrophic hormone (ACTH) action [22].

4.1. Acne

It is a polymorphic dermatitis sustained by a chronic inflammatory process of the hair follicle. In the genesis of acne, four pathological events are distinguished: follicular channel hyperkeratosis, sebaceous hypersecretion, bacterial proliferation, and inflammation.

Chronic hyperandrogenism causes an increase in sebaceous secretion, thus forming a cystic collection resulting in bacterial overlap and thereby stimulating the inflammatory process. It has been estimated roughly that one-third of PCOS patients have acne [23, 24].

4.2. Infertility

The main cause of infertility in PCOS women is chronic anovulation. However, subfertility may be related to the increase of plasma LH levels in the follicular phase of the cycle, causing a resumption of the second meiotic division of the oocyte and the release of premature

ovocytes [25]. High levels of luteinizing hormone (LH) found in polycystic ovary syndrome seem to be related to increased frequency of spontaneous abortions. Other factors that connect PCOS and spontaneous abortion are not yet well known; however, various factors involved in steroidogenesis, folliculogenesis, oocyte maturation, and reduced endometrial receptivity contribute to this vicious cycle between PCOS and abortion [26].

4.3. Insulin resistance and hyperandrogenism in PCOS

There are numerous evidence that polycystic ovary syndrome (PCOS) is a disorder characterized by insulin resistance and hyperinsulinemia.

Insulin resistance is a condition for which a normal insulin concentration produces attenuated biological effects in cases where pancreatic function is intact, leading to compensatory hyperinsulinemia. The presence of insulin resistance does not imply systematic glucose intolerance, and blood glucose may be normal.

Prospective and retrospective observational studies show that at least 40% of women with PCOS exhibit glucose intolerance and that in the 10–20% will develop type 2 diabetes mellitus later in their life between the age of 55 and 65 years [27, 28].

Prior to the development of glucose intolerance, the defect of insulin secretion may remain latent and only occur in conditions that increase insulin resistance, such as the onset of gestational diabetes or a glucose intolerance in the case of corticosteroid treatment.

The molecular mechanism responsible for insulin resistance in PCOS appears to be unique and specific for this syndrome and different from the one present in obesity. Altered phosphorylation of the insulin receptor has been described, resulting in a lack of signal transduction [29].

The ovarian tissue in women with PCOS remains sensitive to the action of insulin, although there is a systemic resistance to insulin.

Ovarian stimulation seems to involve a signal transduction system other than glucose transport, in particular a different second messenger, probably inositol phosphoglycan [30, 31].

Insulin and insulin-like growth factor 1 (IGF-1) are important regulators of ovarian function and directly and indirectly affect ovarian steroidogenesis and androgenic status. Insulin acts directly on the ovarian cells of the theca by activating cytochrome P450 c17 α hydroxylase and 17,20-lyase activity (key enzyme in the synthesis of androgens) and also synergistically promotes the synthesis of androgen induced by the LH.

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

Finally, insulin may suppress liver synthesis of IGF-1-binding protein (IGFBP-1), thereby increasing the bioavailability of IGF-1, another important regulator of androgenic ovarian synthesis. It also appears that insulin may act at the hypothalamus level by modifying the pulsed secretion of LH, thus also affecting ovarian steroidogenesis (**Figure 1**) [32, 33].

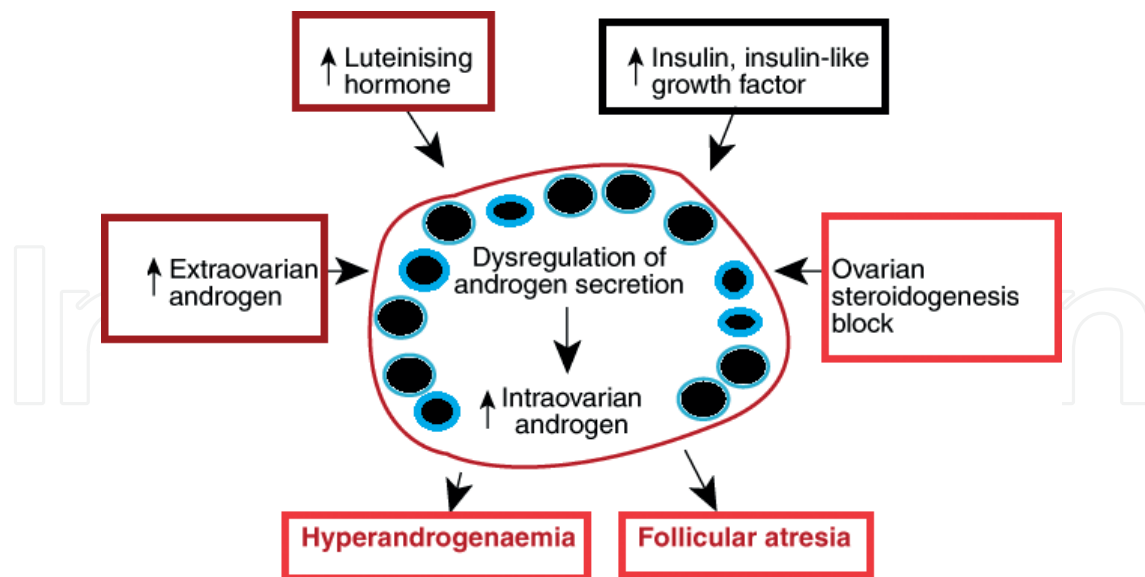


Figure 1. Factors involved in altering follicular steroidogenesis.

There is currently no insulin resistance screening test, whereas a criterion for defining metabolic syndrome has been established that includes components associated with insulin resistance syndrome including visceral obesity, hypertension, fasting hyperglycemia, and dyslipidemia [34]. Other groups add the oral glucose tolerance test (OGTT) to evaluate the fasting blood glucose and at a distance of 2 hours after an oral dose of 75 g of glucose [34].

These characteristics make women with PCOS at increased risk of metabolic syndrome, defined in the past as X syndrome or insulin resistance syndrome [35]. Metabolic abnormalities 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. The metabolic disorders linked to insulin resistance usually become predominant with age advancement (**Figure 2**).

The most common metabolic disorders are those that are traditionally linked to insulin resistance and usually become predominant with age advancement.

4.4. Role and issues of ultrasound in the diagnosis of PCOS

Initially, Adams's ultrasound criteria have been used for ultrasound assessment of the ovaries in women with PCOS which required 10 or more follicles with a diameter of 2–10 mm around an hyperechogenic stroma [37, 38]. Although they are still the most widely used, Adams' criteria are not universally accepted for the diagnosis of polycystic ovary basically because there is a considerable overlap between the normal ultrasound aspect and that of polycystic ovaries regarding the number of follicles and the size of the ovaries, and therefore no reliable cutoff has been identified with satisfactory sensitivity and specificity.

Transvaginal ultrasound is the most commonly used for diagnosis of polycystic ovary (PCO). Ultrasound criteria were subsequently modified resulting in increased ovarian volume ($>10 \text{ cm}^3$) and the presence of >12 follicles in diameter of 2–9 mm in at least one ovary for PCOS diagnosis [39].

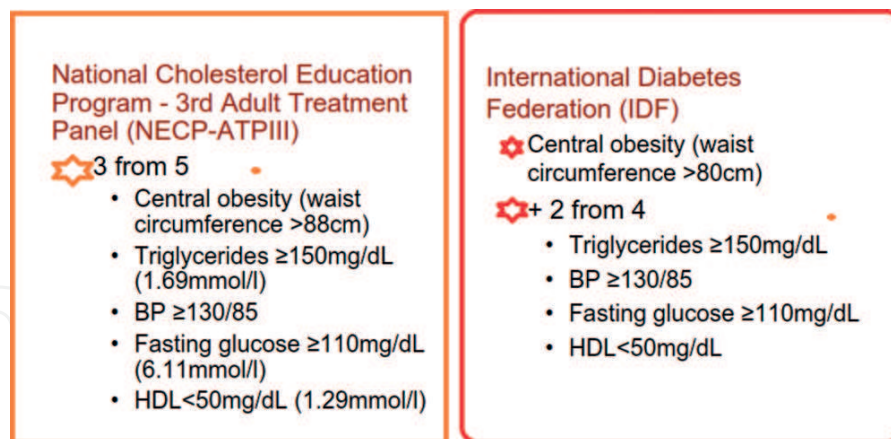


Figure 2. Criteria for metabolic syndrome [36].

Women who use oral contraceptives should be excluded from this criterion as they modify ovarian morphology in healthy women and probably even in women with polycystic ovary [2].

The prevalence of polycystic ovary depending on the age of women: 21.6% in women <35 years and 7.9% in women >35 years [40].

The ultrasound aspect of polycystic ovary can be an isolated finding in asymptomatic patients as well as patients with typical clinical and biochemical manifestations of PCOS may have morphologically normal ovaries.

The variability of the ultrasound description of ovarian morphology (number and location of follicles, hyperechogenic stroma) is a fact even though recent studies consider the increase in ovarian volume ($>10\text{ cm}^3$) as the most reliable criterion for ultrasound evaluation of PCOS [41].

The characteristic ultrasound feature is an increase in ovarian stroma vascularization at Doppler ultrasound [42, 43], which in turn may be related to changes in ovarian morphology. It is necessary to clarify the correlation between ovarian volume and stromal vascularization with ovarian steroidogenesis in patients with PCOS. It is believed that vascular endothelial growth factor (VEGF) plays an important role in increasing stromal flow in patients with PCOS (**Figure 3**) [44].

4.5. Combined oral contraceptive pills in PCOS patient

Combined oral contraceptives (COC) are the most widely used therapeutic option for treating menstrual irregularities. Oral contraceptives cause suppression of LH, resulting in a reduction in androgenic ovarian secretion. The estrogenic component of the combined oral contraceptive induces an increase in sex hormone-binding globulin (SHBG) hepatic synthesis. The various progestogen components of the COC have different effects on the circulating levels of the SHBG [45]. Combined oral contraceptives also significantly reduce the risk of endometrial cancer [45].

The COC pills containing ethinylestradiol and a progestogen with antiandrogenic activity (cyproterone acetate or drospirenone) are effective for the treatment of hirsutism in women

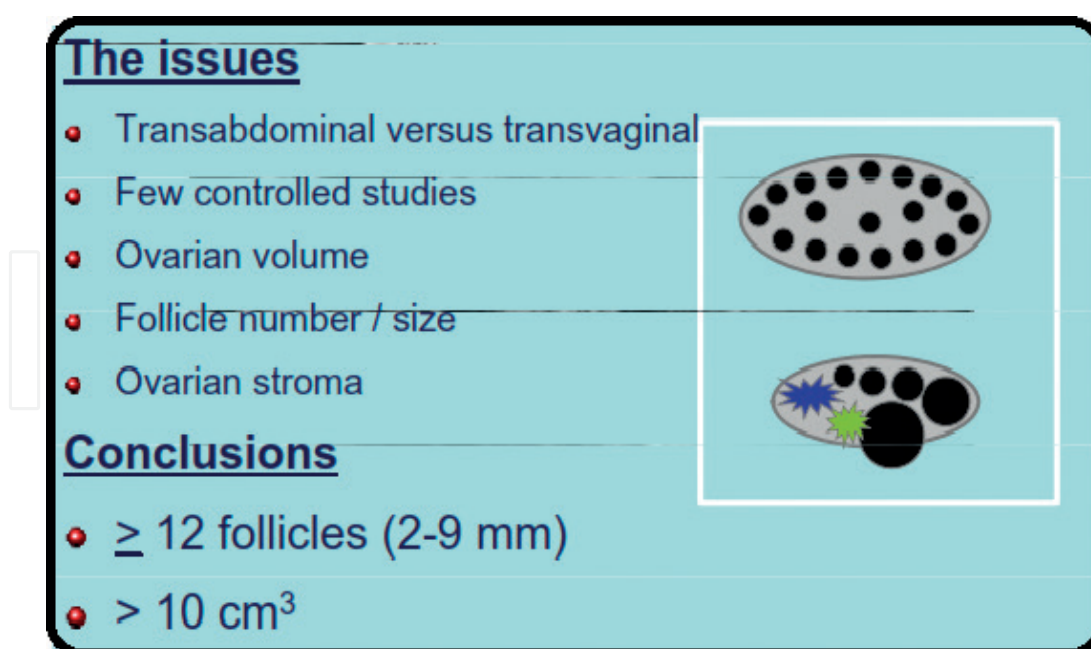


Figure 3. Ultrasound assessment of the polycystic ovary: international consensus definition [39].

with PCOS. The duration of this treatment for at least 6 months is related to the long physiological duration of the hair follicle, while the effect on acne is faster [46].

The best combined oral contraceptive for patients with PCOS is still not well identified. Recent studies have shown that COC therapy may at least partly cause a further worsening of insulin sensitivity in PCOS patients despite a significant reduction in circulating androgens [47, 48].

The effect of COC on insulin balance in women with PCOS remains uncertain. Although the use of combined oral contraceptives is not associated with increased risk of type 2 diabetes mellitus in the general population, studies in women with PCOS have shown mixed results, and this risk cannot be excluded [49].

4.6. Insulin-sensitizing drugs as new therapeutic approach in PCOS

In recent years, numerous studies have been conducted on the use of insulin-sensitizing drugs such as metformin in women with PCOS.

Considering the evidence that insulin resistance and hyperinsulinemia would play a pathogenic role in the development of polycystic ovary syndrome. Metformin improves insulin resistance by reducing glucose intestinal absorption and gluconeogenesis. It also increases the circulating levels of SHBG and FSH with improved ovarian steroidogenesis and normalization of follicular growth [50].

A systematic review evaluated the effectiveness of insulin-sensitizing drugs in women with PCOS. Metformin administration in women with PCOS is associated with a reduction in serum insulin levels and free and total testosterone levels [51]. In short-term therapies (3–6 months), it promotes spontaneous ovulation [51]. There is a decrease in blood pressure

and LDL cholesterol, whereas the effect on body mass index is not significant [51]. Insulin-sensitizing drugs seem to improve some of the clinical parameters of PCOS, but there is not enough evidence of their safety and efficacy in long-term therapies [51].

4.7. Endometrial hyperplasia and the risk of endometrial cancer in PCOS patient

The presence of chronic anovulation leads to an increase of estrogen levels which, over the years, can lead to endometrial hyperplasia and increased risk for endometrial cancer [52].

In women with PCOS, there may be obesity and type 2 diabetes mellitus, two conditions associated with increased risk for endometrial cancer.

Women suffering from PCOS and severe oligomenorrhea (interval of more than 3 months between menstruations) or amenorrhea, a cyclic treatment for 12 days with a progestogen to induce bleeding every 1–3 months [53]. It also recommended a hysteroscopy and endometrial biopsy in the case of ultrasound thickening of the endometrium [53].

5. Conclusions

The natural history of the polycystic ovarian syndrome and the role of possible extra-ovarian factors such as obesity, insulin resistance, and environmental factors in the manifestations of the phenotype of PCOS are the subject of scientific debate.

The sonographic finding of polycystic ovary (PCO) appearance, even if isolated, needs more attention in its clinical evaluation.

Polycystic ovary (PCO) pathogenetic evolution toward a PCOS phenotype is not yet well codified. The pathogenesis of PCOS and its natural history are the determining factors for a real assessment of PCOS. However, longitudinal studies are needed to better clarify the pathophysiology of PCOS and its impact on reproductive health.

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