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Polycystic Ovary Syndrome: Etiopathogenic and Diagnostic Advances

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Abstract

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder in women of childbearing age, characterized by hyperandrogenism, dysovulation and menstrual cycle disorders. Numerous scientific works report the involvement of multiple factors in its pathogenesis which remains even less clear. The international recommendations formulated in a concerted manner by several scientific organizations call for a diagnostic approach to the disorder based on a rigorous evaluation integrating the analysis of the clinical history, a methodical and careful exploration on the hormonal and morphological level. The diagnostic criteria established in 2003 by the group of experts at the Rotterdam conference remain to be considered. However, the ultrasound criterion must be defined considering the improved performance of the ultrasound device. A significant cardiometabolic risk as well as the psychological disorders often associated with PCOS must be considered in the management strategy which is multidisciplinary, and patient centered.

Keywords

Polycystic Ovaries, Hyperandrogenism, Etiopathogenesis, Diagnosis

1. Introduction

Polycystic ovary syndrome (PCOS) is a particularly common endocrine disorder

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in young women of childbearing age, responsible for infertility due to ovulation disorders and hyperandrogenism. It was first described in 1935 by Stein and Leventhal by the association of amenorrhea, hirsutism and infertility [1] [2].

Its prevalence varies from 8 to 13% depending on the population studied and the diagnostic criteria used. According to the World Health Organization, around 70% of cases of this disorder go undiagnosed [3] [4].

PCOS is responsible for infertility due to ovulation disorders and hyperandrogenism. It is frequently associated with insulin resistance, cardiometabolic complications, psychological repercussions and an increased risk of endometrial cancer [5].

Its pathophysiology is complex and still poorly understood, involving hyperandrogenism and hyperinsulinism under influence of multiple factors (genetic, hormonal, environmental) [6] [7].

Diagnosis of PCOS is based on the existence of Clinical and/or biochemical hyperandrogenism, Oligo-Anovulation, polycystic ovarian morphology, after exclusion of other etiologies of hyperandrogenism and ovarian dysfunction (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome) [4] [8].

In 2003, the Rotterdam Consensus defined the diagnostic criteria for PCOS integrating ultrasound data taking into account the performance of ultrasound imaging at the time. Considering the existence of a heterogeneous diagnostic assessment and management of PCOS, recommendations based on international consensus, based on scientific evidence concerning the diagnosis, assessment and management of PCOS were established in 2018 by several scientific organizations including the National Health and Medical Research Council (NHMRC), the Australian Centre for Research Excellence in PCOS (CRESPCOS), the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) [9].

Also, many scientific studies have reported the existence of an increased risk of developing cardiovascular and metabolic disorders in patients with PCOS [9] [10].

In response to persistent cases of diagnostic delay and existence of unmet needs in patients with PCOS, new evidence-based recommendations for the assessment and management of PCOS were developed in 2023 and approved by consensus in five guideline panels [4].

In this article, we report an update on data on the etiopathogenesis and diagnosis of PCOS.

2. Etiopathogenesis

2.1. Etiological Factors

The etiopathogenesis of PCOS is still not entirely clear [8].

Several scientific studies suggest that there is no single etiological factor responsible for the disorder, but rather a number of factors, including ovarian dysfunction with increased androgen production and abnormal folliculogenesis, insulin resistance, fetal development, genetic and environmental factors [7] [8].

These etiological factors include:

- Intraovarian factors: inhibin, anti-Müllerian hormone (AMH)
- Extra-ovarian factors:
  - Hormonal: at the central level, this involves pituitary luteinizing hormone (LH) and peripheral insulin and inositols [8].
  - Genetics: the possible role of the involvement of the genetic factor in the pathogenesis followed a series of scientific studies showing the existence of familial clustering of cases with a high prevalence of PCOS in first-degree relatives and sometimes significant heritability in certain families [8]. Several candidate genes have been studied in search of an association between their variants or anomalies (translocation, deletion, inversion, addition) and the risk of occurrence of PCOS. These are genes or their variants involved in the development of insulin resistance and obesity phenomena (FTO, MCR4, PPAR, INSR1 genes, etc.), androgen production (CYP11A, CYP19, CYP1A1, SRD5A2 genes, etc.) or folliculogenesis disorders (FBN3 gene, etc.). Despite these studies, no causal link with PCOS has been clearly proven. Genome-wide association studies would be necessary and could help to better understand the contribution of genetics in the pathophysiology of PCOS [7] [8].
  - Epigenetic factors occurring during fetal development, such as intrauter ine exposure to excess AMH, androgens or toxins (bisphenol-A, endocrine disruptors, etc.) may be the etiologic mechanism behind PCOS. These factors are likely to cause some changes in a chromosome showing stable heritable phenotypes without actual alterations in the DNA sequence [8].
  - Environmental factors include physical inactivity, obesity, unhealthy eating habits as well as eating junk food high in fat, salt, sugar, advanced glycation end products (AGEs). These factors have a vital role in the development and progression of PCOS. These factors play a vital role in the development and progression of PCOS [6] [11].

2.2. Pathogenesis

The pathogenesis of PCOS is still not completely clear to this day. The above-mentioned etiological factors are thought to be responsible for increased androgen production and abnormal folliculogenesis. Ovarian-related hyperandrogenism represents the primary pathogenic mechanisms of PCOS [7] [12].

At the intra-ovarian level, the hyperproduction of androgens would be related to dysregulation at the level of theca interna cells, stimulation of androgen secretion at the level of theca cells secondary to the paracrine effect of inhibin and excess anti-Müllerian hormone (AMH) responsible for stopping follicular growth [13] [14].

At the extra-ovarian level, hyperandrogenism is increased by hyperinsulinemia and the secretion of luteinizing hormone (LH) directly stimulating this production. Indeed, the elevation of LH would not be the primary causal abnormality of PCOS but rather a consequence of the alteration of the negative feedback control of androgens on the hypothalamic-pituitary axis **[13]**.

Hyperinsulinemia leads to stimulation of intra-ovarian androgen production by

promoting the synthesis or activity of enzymes involved in steroidogenesis. In addition, it contributes to the increase in the free fraction of androgens by decreasing their transport protein, which is Sex Hormone Binding Globulin (SHBG). It would also promote stimulation of pituitary LH production as well as inhibition of hepatic production of Insulin-like Growth Factor Binding Proteins (IGFBP)-1, thus increasing the bioavailability of IGF (Insulin-like Growth Factor) which can stimulate ovarian steroidogenesis [7] [14].

Some authors advocate the possibility of "in utero reprogramming" of the fetal ovary which would be genetically programmed for spontaneous hyperproduction of androgen [13] [14].

Furthermore, myo-inositol deficiency appears to be involved in the genesis of insulin resistance, which is an aggravating factor in PCOS. Indeed, considered as a second messenger of insulin in the muscle, myocardium and liver, inositols play an important role in the genesis of insulin resistance. Indeed, there are 9 stereoisomers of inositols, two of which play an important but very different role. D-chiro-Inositol (DCI) promotes the synthesis and storage of glycogen, while myo-inositol (MI) promotes its consumption. The transformation of MI into DCI occurs at the level of hepatocytes under the action of epimerase, the rate of which is proportional to that of DCI. The activity of epimerase is stimulated by insulin. At the ovarian level, MI promotes ovulation and the development of follicles. MI deficiency is deleterious to the granulosa and the oocyte, while excess DCI decreases the effect of FSH, follicular growth and increases AMH. Hyperinsulinemia promotes the transformation of MI into DCI, blocks ovulation and ovarian function [7] [12].

2.3. Consequences

Folliculogenesis Disorders

They characterize PCOS and are explained by two major phenomena, in particular excessive and premature follicular growth affecting class 1 to 5 follicles, which appears to be the consequence of an in situ trophic effect of ovarian androgens produced in excess [2] [5].

The second phenomenon is a defect in the selection of the dominant follicle characterized by the absence of complete pre-ovulatory maturation of a single follicle. This anomaly in the process of follicular selection-dominance is responsible for an accumulation of immature follicles in the ovarian stroma and would be due to the lack of action of FSH on the cohort of follicles and to a premature action of LH [8].

3. Clinical Study

PCOS is a heterogeneous pathology in terms of phenotypic and metabolic consequences. Different phenotypes have been described by numerous authors throughout the literature. This phenotypic approach to classifying PCOS provides a simple diagnostic tool while avoiding the need to choose between several different definitions of PCOS [15] [16].

4 phenotypes have been described [9] [16], including:

- The classic phenotype, combining clinical hyperandrogenism, oligo-ovulation, insulin resistance and more severe metabolic disorders;

- Ovulatory PCOS marked by hyperandrogenism, polycystic ovarian morphology on ultrasound, insulin resistance and metabolic pathologies;

- The non-hyperandrogenic phenotype with oligo-ovulation, polycystic ovarian morphology on ultrasound with a weak association with insulin resistance and metabolic co-morbidities (Table 1).

Table 1. Polycystic ovarian syndrome phenotypes [9] [16].

Parameter	Phenotype A	Phenotype B	Phenotype C	Phenotype D
Hyperandrogenism	+	+	+	-
Ovulary dysfunction	+	+	-	+
Polycystic ovarian morphology	+	-	+	+

3.1. Typical Form

Clinical

Signs related to chronic oligo-anovulation

Oligo/anovulation is manifested by menstrual cycle disorders, which are characteristically long-standing in patients with PCOS. These disorders are frequent in the three years following puberty. Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of PCOS [4], described a definition of these disorders adapted to the pubertal period (Table 2).

Table 2. Definition of menstrual cycle disorder [4].

Definition of menstrual cycle disorder
1 - 2 years post-menarche (after first menstrual period): duration < 21 days or > 45 days
> 1 year Post-menarche: Any cycle > 90 days
> 3 years post-menarche to peri-menopause: duration < 21 days or > 35 days or less than 8 cycles per year
Primary amenorrhea at age 15 or > 3 years after thelarche (breast development)

Prolonged use of estrogen-progestins can mask this cycle disruption. These disorders can be of the type of long cycle or spaniomenorrhea (≤ 8 menstrual episodes per year), oligomenorrhea, secondary amenorrhea or rarely primary amenorrhea. However, cycles can also be regular. The presence and long-standing nature of cycle disorders in young women should prompt a diagnosis of PCOS. Dysovulation is often responsible for infertility in PCOS [4] [17].

Signs of hyperandrogenism

They are the translation of excessive ovarian production of androgens. They can manifest as hirsutism defined by excessive hairiness made of hard and pig-

mented hairs, reminiscent of a masculine appearance, in areas normally hairless in women (face, back, white line, thorax, inner and posterior sides of the thighs). Its evaluation is made by the Ferriman and Gallwey score which is subjective and considered pathological for a value greater than or equal to eight [2] [18].

Other signs are hyperseborrhea androgen-dependent characterized by oily skin and hair, which are related to significant sebum production and acne. Acne is inconsistent, often common and frequent during adolescence, inflammatory type, significant, with masculine topography and affecting at least two different sites [18] [19].

The existence of signs of virilization (clitoral hypertrophy, alopecia of the temporal gulfs, hoarseness of the voice, muscular hypertrophy with sometimes a masculine morphotype) are very rare in PCOS and should lead to the search for an organic cause of hyperandrogenism, particularly tumoral (ovarian or adrenal) [20].

Paraclinical

Hormonal exploration in a patient suspected of having PCOS should include an assessment of ovarian secretion and gonadotropic axis function, despite mandatory measurement of 17 OH progesterone and prolactin.

Hormone dosages should be carried out between 8 and 10 a.m., at the start of the follicular phase or after a short progestin treatment and in the absence of corticosteroid therapy [2] [8].

Assessment of ovarian secretion

The search for biological hyperandrogenism is based on the first-line determination of total testosterone levels, the moderate elevation of which is frequent and seems characteristic of PCOS. Any high testosterone level result greater than 1.5 ng/ml should lead to questioning the diagnosis of PCOS and to discussing an organic tumor cause (ovarian or adrenal). This total testosterone level measurement nevertheless presents an imperfection with the possibility of false negatives in 20 to 60% of cases, hence the interest in sometimes considering the measurement of free testosterone, not linked to the SHBG protein, which is the most sensitive indicator but a direct measurement less used in current practice. The calculation of the free testosterone index (ITL) can be carried out by considering the results of the measurement of total testosterone (T) and SHBG using the formula: ITL = T/SHBG × 100. A dosage of Δ 4-androstenedione showing a result greater than 2 ng/ml with radioimmunological measurement or after chromatography coupled with mass spectrometry, is suggestive of PCOS, in the absence of the enzymatic block in 21 hydroxylases. The inconstant secretion of Δ 4-androstenedione by the cells of the theca interna does not allow it to be a good biological marker of ovarian hyperandrogenism [2] [3] [5].

Estradiol measurement in patients with PCOS showed a result close to normal women in the early follicular phase. However, a loss of estradiol cyclicity has been reported. Its measurement in the context of PCOS helps to make a differential diagnosis of cycle disorders (ovarian insufficiency, hypogonadotropic hypogonadism) [21].

The dosage of progesterone in the 2nd^{part} of the cycle (22 - 24th^{day}) will allow, in

the event of cycle regularity, to confirm the ovular nature by showing a result higher than 2.5 ng/ml in the event of ovulation) [1] [21].

Assessment of exocrine function in PCOS generally shows normal levels of inhibin B suggesting the absence of essential contribution of this marker in the diagnosis of PCOS.

anti-Müllerian hormone (AMH) has shown a high level in patients with PCOS and seems to indicate the significant presence of preantral follicles. This dosage is of diagnostic assistance especially in mildly symptomatic forms of PCOS or in cases of non-discriminatory ultrasound data [5] [22]. However, the international consensus [9] does not recommend the dosage of AMH as a first-line measure in the diagnosis of PCOS.

3.2. Gonadotropin Dosage [14]

The increase in the basal LH rate is a characteristic observed in PCOS and would be the consequence of an increase in the amplitude and frequency of its pulses. This seems to be linked with a primitive alteration of the functioning of the gonadotropic axis [21] [22].

However, a normal baseline LH value can be observed during PCOS.

The study of LH pulsatility is cumbersome to implement and reserved for research protocols. It has not shown any diagnostic superiority over the basic dosage.

Baseline FSH measurement does not appear to provide essential diagnostic information for PCOS, since it is often normal at the beginning of the follicular phase.

On the other hand, when combined with estradiol dosing, it will eliminate other causes of cycle disorders such as gonadotropic deficiency [22] [23].

3.3. Morphological Criteria

Ultrasound assessment in the context of PCOS diagnosis should be performed by an experienced operator at the beginning of the cycle (between the 2nd and 5th day). It consists of performing a suprapubic ultrasound during the first step for an analysis of internal genital organs (uterus and ovaries) and to specify the existence of an ovarian anomaly or tumor. The second step corresponds to an ovarian exploration by endovaginal route (unless the patient refuses or the patient is a virgin) using a high-frequency probe (> 6 MHz) for good spatial resolution [24] [25].

In 2003, the Rotterdam consensus defined the ultrasound criterion for the diagnosis of PCOS as the presence of at least 12 follicles of 2 to 9 mm in diameter per ovary and/or an ovarian volume of more than 10 cm^3. The emergence of new, more efficient ultrasound devices, offering better resolution, distinguishing small follicles of less than 2 mm in diameter, has led many authors to re-evaluate the ultrasound criterion defined by the Rotterdam consensus [5] [26].

After a comparative study including 62 patients with PCOS and 66 controls, Dewailly *et al.*, in 2011, re-evaluated the follicle count, increasing it to 19 per ovary

for the diagnosis of PCOS with an ovarian volume of 7 cm^3 [27]. Lujan's team, for its part, increased the antral follicle count (AFC) per ovary to 26 for the ultrasound definition of PCOS by using in their study a control group made up of asymptomatic patients with ultrasound-based PCOS [28].

A definition of new ultrasound criteria in the diagnosis of PCOS was made by Dewailly *et al.* [19] bringing the antral follicle count to at least 25 during an evaluation by an ultrasound device equipped with a maximum endovaginal probe frequency greater than 8 MHz. This CFA threshold nevertheless remains operator and device dependent.

The 2018 ESHRE international consensus set the CFA threshold at 20 follicles [9].

It maintains the ovarian volume threshold of 10 cm^3, used in the diagnosis of PCOS when ultrasound assessment does not allow for an accurate count of antral follicles or when the use of the endovaginal probe is not possible.

If, for technical reasons, the endovaginal route is impossible, and the suprapubic ultrasound is not precise, MRI is more effective, including for ovarian volume. MRI can describe the morphology of the PCOS ovary: ovarian volume ≥ 10 cm^3, follicle size < 9 mm with a threshold not yet formally established, and peripheral distribution of follicles. Fondin, comparing 55 pubescent adolescents aged 11 to 18 with PCOS and 55 controls, found a very good correlation between these three criteria and the clinical and biological picture of PCOS. They mentioned a threshold of follicles < 9 mm of 28 on one of the two ovaries in this population [9]. MRI seems to be a valuable tool, particularly for persistent cycle disorders in overweight girls or in cases of hyperandrogenism.

In 2023, recommendations from international evidence-based guidelines for the evaluation and management of PCOS retain as the primary ultrasound criterion for the diagnosis of PCOS in adults, the presence of at least 20 follicles during endovaginal ovarian exploration using a high-frequency probe (8 MHz). Alternative criteria are an ovarian volume ≥ 10 mL or a number of follicles per section ≥ 10 [4] [5].

Abdomino-pelvic ultrasound is routinely suggested in post-menopausal women to rule out the presence of a tumor. However, it is not necessary in the case of cycle disorders with hyperandrogenism in pre-menopausal women. Abdomino-pelvic ultrasound is of little help, or even unnecessary, in adolescent women, given the frequent presence of multi-follicular ovaries during the first 8 years post-menarche [4] [25].

4. Clinical Forms

4.1. Comorbidities Associated with PCOS

Comorbidities and abnormalities are often associated with PCOS [26] [27]. These include:

- Obesity: which contributes to worsening dysovulation, hyperandrogenism and

the risk of metabolic syndrome;

- Insulin resistance: common, even in patients with a normal body mass index. It exposes to the risk of developing metabolic abnormalities with impaired glucose tolerance. It is thought to be the result of primary abnormalities of the insulin receptor resulting from mutations or autoantibodies to insulin receptors. Clinical markers of insulin resistance such as acanthosis nigricans or lipodystrophy should, therefore, be sought in any patient with PCOS;
- Metabolic syndrome: frequently associated with PCOS, favored by obesity and insulin resistance (**Table 3**).

Table 3. Definition of metabolic syndrome [26].

Criteria	Definition according to IDF/AHA/NHLBI (2009)
	Three of the following five criteria
Waist size	≥ 94 cm in men and ≥ 80 cm in women (for sub-Saharan African populations) ≥ 94 cm in men and ≥ 80 cm in women (for Europeans)
High triglycerides (HT)	>1.5 g/l or ongoing treatment for hypertriglyceridemia
HDL-C Low	<0.4 g/l in men and < 0.5 g/l in women
Blood pressure (BP)	PAS ≥ 130 mm Hg and/or PAD ≥ 85 mm Hg or anti-hypertension treatment
Fasting blood sugar	≥ 1 g/l or ongoing treatment for diabetes mellitus

IDF = International Diabetes Federation. AHA = American Heart Association. NHLBI = National Heart, Lung, and Blood Institute.

4.2. Paucisymptomatic Form

The diagnosis of PCOS can be difficult in certain forms of non-typical clinical presentation. Indeed, some patients, especially adolescents, with authentic PCOS may present clinically only hirsutism without cycle disorder or secondary amenorrhea or isolated chronic dysovulation. The hormonal assessment may also be non-contributory if a normal blood level of testosterone, LH or SDHEA is shown. In these conditions, ultrasound can be of essential contribution and will often make it possible to make the diagnosis by objectifying criteria compatible with the diagnosis of PCOS. In the case where the morphological assessment does not provide discriminatory arguments for the diagnosis of PCOS, long-term follow-up with assessment is recommended to look for the appearance of signs and abnormalities in the hormonal assessment, often with a high AMH level [5] [9].

The guidelines formulated by the international consensus to guide clinical practice in the context of PCOS, however, note the required presence of oligo or anovulation and hyperandrogenism in an adolescent in the diagnosis of PCOS and do not recommend the essential performance of diagnostic ultrasound in this context [26] [28].

4.3. Complications or Risks Associated with PCOS

The presence of PCOS exposes you to a number of risks [27] [29], including:

- Risk of cardiovascular diseases: favored by the existence of insulin resistance, metabolic syndrome and obesity with a possible occurrence of hypertension, coronary pathology, strokes and venous thrombosis;
- Diabetes intolerance or type 2 diabetes mellitus: logical corollary of insulin resistance;
- Dyslipidemia: metabolic abnormality with often a typical profile of insulin resistance state associating: increase in triglyceride and LDL cholesterol levels and decrease in HDL cholesterol levels;
- Sleep apnea syndrome: which can be life-threatening for the patient;
- Non-alcoholic metabolic steatopathy or NAFLD (non-alcoholic fatty liver disease): favored by the state of insulin resistance and metabolic disorders. In the absence of appropriate management, it can evolve into the stage of steatosis-hepatitis (NASH) which has a risk of progression to cirrhosis or hepatocellular carcinoma;
- Infertility: results from ovulation disorders frequently observed in PCOS;
- Obstetrical risks: they have been reported in patients with PCOS including spontaneous miscarriages, pregnancy-induced hypertension and preeclampsia, gestational diabetes, premature delivery;
- Cancerization: A marked prevalence of certain cancers has been reported in patients with PCOS. These include the risk of developing endometrial hyperplasia or adenocarcinoma resulting from relative hyperestrogenism favored by hyperinsulinemia, LH hypersecretion with dysovulation; and ovarian cancer;
- Psychiatric disorders such as anxiety, depression, eating disorders and bipolar disorder observed in patients with PCOS.

5. Diagnosis

5.1. Positive Diagnosis

The diagnosis of PCOS depends on a careful assessment of hyperandrogenism, ovulatory function, and ovarian morphological data [4] [27].

Over the past three decades, a number of medical societies, healthcare institutions and research organizations have put forward proposals concerning the diagnostic criteria for PCOS. They all specify that the diagnosis of PCOS can only be made after exclusion of other causes of hyperandrogenism or dysovulation (congenital adrenal hyperplasia, cushing's syndrome, androgen-secreting tumors, hyperprolactinemia...) [9] [16].

Diagnostic criteria for PCOS were first described in 1990 at a conference of the National Institute of Child Heath and Human Development (NIH) in the USA. PCOS was diagnosed on the basis of 2 criteria: clinical or biochemical hyperandrogenism and chronic oligo-anovulation [16] [30].

The second definition of PCOS diagnosis was established following the consen-

sus of 27 PCOS experts at a conference in Rotterdam, the Netherlands in May 2023. The conference was supported by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) [24].

Novelty in the consensus was the addition to the NIH 1990 criteria of ultrasound characteristics, in particular the morphology of polycystic ovaries. The Rotterdam Consensus [4] defined PCOS as the existence of two of the three criteria: clinical and/or biological hyperandrogenism, oligo- and/or anovulation, and ultrasound morphology of polycystic ovaries.

Application of the Rotterdam consensus criteria had led to a substantial increase in number of patients diagnosed with PCOS, with a widening of the heterogeneity of PCOS phenotypes [16] [24].

In 2006, a working group assembled by the Androgen Excess & PCOS Society (AEPCOS), comprising American, European and Australian researchers, conducted a systematic review of the literature to study and analyze links between different PCOS phenotypes and independent morbidity. The conclusion of their work was that PCOS is a disorder resulting primarily from androgen excess. It should be diagnosed by the presence of clinical or biochemical hyperandrogenism associated with ovarian dysfunction [16] [30].

The diagnostic criteria for PCOS from the Rotterdam conference were approved in international consensus guidelines in 2018. These guidelines had nevertheless incorporated technological advances in ultrasound equipment into the definition of the ultrasound criterion. They indicated that ultrasound data were not required for diagnosis of PCOS if the first two criteria (hyperandrogenism and oligo/anovulation) were present [9].

The threshold for antral follicle count (AFC) per ovary was 20 follicles when endovaginal ultrasound was performed with a high-frequency probe [9].

Table 4. Evolution of PCOS diagnostic criteria **[4]** [9] [16].

DEFINITION	NIH 1990	ESHRE/ASRM 2003	Androgen Excess-PCOS Society 2006	International Guidelines 2018	Internationales 2023
Criteria	1-Clinical or biochemical hyperandrogenism 2-Oligo-Anovulation	1-Clinical or biochemical hyperandrogenism 2-Oligo-Anovulation 3-Polycystic ovarian morphology (>12 follicles of 2 to 9 mm in diameter per ovary)	1-Clinical or biochemical hyperandrogenism 2-Ovarian dysfunction (Oligo-Anovulation or Polycystic ovarian morphology)	1-Clinical or biochemical hyperandrogenism 2-Oligo-Anovulation 3-Polycystic ovarian morphology (≥20 follicles and/or an ovarian volume of more than 10 cm^3)	1-Clinical or biochemical hyperandrogenism 2-Oligo-Anovulation 3-Polycystic ovarian morphology. ≥20 follicles per ovary. Alternative criteria: ovarian volume ≥ 10 mL or number of follicles per section ≥ 10.
Conditions of diagnosis	2 of 2 criteria required	2 of 3 criteria required	2 of 2 criteria required Exclusion of other etiologies	2 of 3 criteria required	2 of 3 criteria required

NIH: National Institues of Health. ESHRE: European Society for Human Reproduction an Embryology. ASRM: American Society for reproductive Medecine. PCOS: Polycystic Ovarian Syndrome.

In 2023, recommendations from the international evidence-based guidelines for the evaluation and management of polycystic ovary syndrome [4] [5] specified that the diagnosis of PCOS can be supported by the existence of at least 2 of the following criteria:

- oligo or anovulation;
- Clinical and/or biological hyperandrogenism;
- Polycystic ovary morphology on ultrasound or elevated antimüllerian hormone (AMH).

The threshold for antral follicle count (AFC) per ovary was 20 follicles. Alternative criteria selected were ovarian volume ≥ 10 mL or number of follicles per section ≥ 10.

The evolution of PCOS diagnostic criteria is summarized in **Table 4.**

5.2. Differential Diagnosis

The diagnosis of PCOS syndrome should only be made after formally eliminating other causes of similar clinical presentation [4].

Thus, considering the clinical picture (cycle disorders, signs of virilization, etc.) the hormonal biological assessment (total testosterone, DHEAS, 17 hydroxy-Progesterone, prolactinemia), certain diagnoses must be sought, after having ruled out any medication (anabolic steroids, valproic acid, synthetic progestins with androgenic effect) which could be responsible for hyperandrogenism [4] [5].

So:

- testosterone levels > 1.5 ng /ml should lead to consideration and investigation of a tumor cause (ovarian or adrenal) responsible for the hypersecretion of androgens [4] [5];

A high DHEAS dosage > 20 µmol/l should lead to a search for an adrenal tumor, especially since the patient presents signs of virilization and a picture of hypercorticism; an adrenal CT scan will be performed in this case **[5]** [20].

- The dosage of 17 OH progesterone allows us to look for an adrenal enzyme block due to 21 Hydroxylase deficiency in its late-onset form. A baseline result > 5 mg/ml confirms the diagnosis, as does a peak greater than 10 mg/ml after a 0.25 mg synacthen test. A genetic study should be considered to look for a heterozygous form of mutation of the CYP21A2 gene, for low values of 17 OH progesterone between 5 and 10 ng /ml after a synacthen test. Some authors suggest an early diagnosis of this disorder in any woman with clinical hyperandrogenism [4] [20].
- A prolactin pathology must also be investigated and eliminated due to the consequences of hyperprolactinemia leading to functional hypogonadotropic hypogonadism with sometimes cycle disorders (amenorrhea, spaniomenorrhea), moderate hyperandrogenism due to adrenal production of androgens (DHEAS). Galactorrhea generally guides the diagnosis in this context and the prolactinemia assay confirms it by ensuring a good quality assay (eliminating macro-prolactinemia) [5] [20].

- Functional hypothalamic anovulation should be considered in the presence of a cycle disorder resulting from functional hypogonadotropic hypogonadism in the context of high-level sports practice, dietary restriction or anorexia nervosa [5] [31] [32].

6. Conclusion

Polycystic ovary syndrome remains a heterogeneous endocrine disorder, particularly common in young women and can cause infertility. Many studies show that this disorder could be of a complex, multigenic origin with epigenetic and environmental influences. This syndrome should be considered and investigated in any young woman with clinical and/or biological hyperandrogenism associated or not with cycle disorders. The Rotterdam criteria remain relevant for the definition of this disorder, however, follicular counting must take into account the more refined quality of ultrasound devices currently used. The 2018 international consensus guidelines and the recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome, remain an interesting source of data guiding the diagnostic and therapeutic approach in the context of PCOS with possible adaptation according to the local practice context.

Conflicts of Interest

We have no conflict of interest regarding this article.

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