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Polycystic Ovary Syndrome: Definitions, Phenotypes and Diagnostic Approach

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Abstract

Polycystic ovary syndrome (PCOS) constitutes a continuum spectrum of symptoms starting from the early prepubertal years and continuing after menopause. The phenotypic expression varies through time, depending on several internal (e.g. ovarian/adrenal steroidogenesis, insulin resistance) and external factors (e.g. quality and quantity of food, exercise). Moreover, the emergence of new definitions with the use of ovarian morphology, besides chronic anovulation and hyperandrogenism, as diagnostic criteria, increased the phenotypic variety of PCOS presentation. In this review, the clinician is provided with useful information regarding grey zones in assessing anovulation, hyperandrogenism, ovarian morphology and the difficulties in differential diagnosis of PCOS. Furthermore, the lack of substantial data characterizing metabolic/hormonal profile and the potential cardiovascular risk in newer PCOS phenotypes, as well as the absence of longitudinal data questioning a possible shift from one phenotype to another are underlined. These notions indicate that despite the initial presentation of a patient with PCOS, close follow-up and therapeutic interventions aiming to reduce long-term cardiovascular risk are warranted.

Polycystic ovary syndrome (PCOS) constitutes the most common endocrinopathy of women of reproductive age. It has gained a great deal of public attention over the last few decades, as this is reflected in over 1,500,000 Internet sites dedicated to the syndrome. However, although widespread, PCOS is a very complex endocrine condition, making its diagnosis a difficult and challenging task in everyday clinical practice. These difficulties in diagnosis, as well as the heterogeneity of the disease and its nebulous nature, were made evident from the very first description of PCOS by Stein and Leventhal. Specifically, among the 7 women described in the original report, a variety of clinical symptoms were observed, such as obesity, hirsutism, acne, and amenorrhea, all of which were associated with enlarged bilateral polycystic ovaries. These distinctive features, displaying a varying degree of expression in each case, emphasize

the phenotypic variability of PCOS and, in fact, explain why it is defined as a syndrome and not a disease.

A syndrome is a cluster of symptoms, which cannot be explained under the prism of a common etiologic factor or a unifying pathophysiological pathway. Furthermore, the fact that hormones act in almost all tissues but at a different rate, this depending on their receptor function and post-receptor signaling, accounts to a considerable degree for the variety of clinical expression observed in hormonal disorders and metabolic aberrations. This situation is further complicated in PCOS in which more than one hormone secretion is modified. More specifically, women with PCOS manifest hyperandrogenemia, hyperinsulinemia, and hypothalamic-pituitary-ovarian axis aberrations, as well as adipose tissue dysfunctional adipokine secretion, all of which interact in different tissues (fat, liver, muscle and ovaries), thus leading to a variety of phenotypes. Due to these difficulties, the definition of PCOS has been a matter of constant debate, and the different combinations of symptoms and signs have through the years resulted in significant variations of diagnosis and management between different groups.

Definitions and Phenotypes

In 1990, the publication of strict National Institutes of Health (NIH) criteria, which make obligatory for the diagnosis the concomitant presence of anovulation and hyperandrogenemia on either the biochemical or the clinical level (hirsutism/acne), underscored the fact that PCOS is a metabolic/reproductive disorder. However, since the common perception was that polycystic morphology (PCOM) was a characteristic finding in these women, the absence of inclusion of ovarian PCOM gave rise to a great many discrepancies on clinical grounds. Although excellent studies have since clearly demonstrated that polycystic ovarian morphology on ultrasound may be found in about 20–30% of normally ovulating, but not hyperandrogenemic women, for a significant number of physicians (especially Europeans), this distinction was mandatory for the diagnosis. This fallacy led in 2004 (Rotterdam) to the formulation of new diagnostic criteria whereby the presence of all these three factors (chronic anovulation, hyperandrogenism, and polycystic ovaries on ultrasonography) was evaluated and PCOS was diagnosed in the presence of two of the three diagnostic criteria. Using the possible combinations of these criteria, four different phenotypes of PCOS are now identified:

- Type A: hyperandrogenism, chronic anovulation and polycystic ovaries.
- Type B: hyperandrogenism and chronic anovulation.
- Type C: hyperandrogenism and polycystic ovaries.
- Type D: chronic anovulation and polycystic ovaries.

These different phenotypes are illustrated in figure 1.

The Rotterdam criteria do not delineate the essential features of PCOS, since they identify PCOM as being equivalent to chronic anovulation and hyperandrogenism

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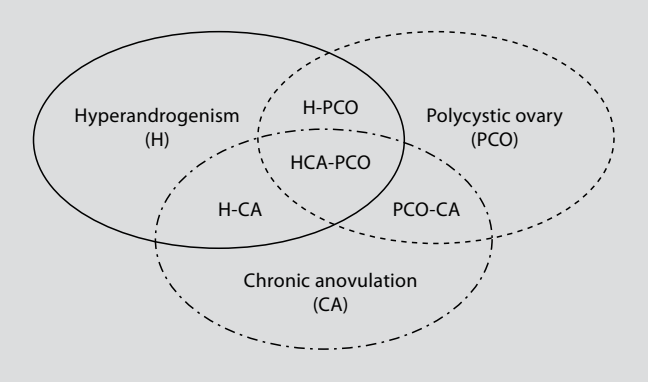

Fig. 1. The different phenotypes in PCOS. Type A: hyperandrogenism, chronic anovulation and polycystic ovaries; type B: hyperandrogenism and chronic anovulation; type C: hyperandrogenism and polycystic ovaries; type D: chronic anovulation and polycystic ovaries.

as regards diagnosis. These criteria, however, laid emphasis on the fact that PCOS could manifest via a spectrum of symptoms, thus implying that it may be diagnosed in the absence of androgen excess. Many authorities in the field questioned this position, and in 2006 the Androgen Excess Society (AES) pointed out that PCOS is basically a hyperandrogenic disorder, and that the existence of hirsutism/acne and/or hyperandrogenemia constitutes a sine qua non for PCOS diagnosis. The second criterion essential for the diagnosis according to the AES is either anovulation or polycystic ovarian morphology. These criteria were further consolidated in 2009 by the Androgen Excess and PCOS Society Task Force statement. All definitions mentioned above are presented in table 1. However, despite the presence of these several definitions, PCOS is still a diagnosis of exclusion of other androgenic entities. Furthermore, none of these definitions has been verified in adolescents in whom anovulation, PCOM, and hyperandrogenism usually occur for a temporary period [1, 2].

Most importantly, it should be stated that these various definitions are products of consensus statements, namely the majority opinion, and not the robust and solid findings of clinical trial evidence. This disadvantage is reflected in the vague nature of the definitions and in the lack of compliance of all medical authorities with these definitions. Moreover, the array of various definitions available in the literature has increased confusion regarding PCOS diagnosis, especially among different specialties. This situation was clearly illustrated in a study conducted by Cussons et al. [3] involving 138 endocrinologists and 172 gynecologists among whom different criteria were used for diagnosis. Specifically, 70% of endocrinologists versus half of the gynecologists considered menstrual irregularity as an essential criterion, whereas 60% of the gynecology group versus 14% of endocrinologists judged polycystic ovaries on ultrasound as an essential tool for PCOS diagnosis. Furthermore, although this study was carried out in 2005, less than 15% of gynecologists would use either the NIH or

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Table 1. Definitions of PCOS

Definition/year	Diagnostic criteria[1]
NIH/1990	Requires the simultaneous presence of: 1. Hyperandrogenism (clinical and/or biochemical) 2. Ovarian dysfunction
Rotterdam (ESHRE/ASRM)/2003	Requires the presence of at least two criteria: 1. Hyperandrogenism (clinical and/or biochemical) 2. Ovulatory dysfunction 3. Polycystic ovarian morphology[2]
AES/2006	Requires the presence of hyperandrogenism (clinical and/or biochemical) and either: 1. Ovulatory dysfunction 2. Polycystic ovarian morphology[2]
Androgen Excess and PCOS Society/2009	Requires the simultaneous presence of: 1. Hyperandrogenism (clinical and/or biochemical) 2. Ovarian dysfunction (ovulatory dysfunction and/or polycystic ovarian morphology[2])

[1] It is important to state that as well as being well established by all the diagnostic criteria available PCOS diagnosis is an exclusion diagnosis of other disorders, such as NC-CAH, Cushing syndrome, acromegaly, hyperprolactinemia, hypothyroidism, premature ovarian failure, virilizing adrenal or ovarian neoplasm and a drug-related condition.
[2] The ultrasound definition of polycystic ovarian morphology is the presence of ≥12 follicles with a 2- to 9-mm diameter on the ovary. An ovarian volume >10 ml is also suggestive. Only one ovary consistent with polycystic ovarian morphology is sufficient for the diagnosis.
ESHRE = European Society for Human Reproduction and Embryology; ASRM = American Society for Reproductive Medicine.

Rotterdam criteria for diagnosis. Although these percentages were higher, they were also not acceptable among endocrinologists (about 40%). These data demonstrate the existing broad discrepancy in PCOS diagnosis, which is reflected in everyday practice. The aim of this review is to provide an overview of the current knowledge concerning the varying phenotypic expression of PCOS according to current definitions as well as a proposal as to which could be the ideal diagnostic approach [3].

Prevalence of Phenotypes Based on Different Criteria

PCOS is considered to be the most common endocrine disorder in women of reproductive age. However, the actual prevalence of PCOS in the community is the subject of a continuing debate due to the specific sampling methodology used in each of the various studies as well as study design limitations. Nevertheless, PCOS prevalence

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based on the NIH criteria is estimated to be about 6–8% in women of Caucasian origin, although with the implementation of the Rotterdam criteria, the prevalence increased to 15–25%, while the use of AES recommendations put PCOS prevalence at about 10–15%. These findings strongly suggest that a thorough understanding of PCOS pathophysiology and its association with reproductive and metabolic disturbances is essential for any physician addressing women's health, since the very large number of patients he/she will encounter will make it more than evident that this concerns a highly multifaceted syndrome [4, 5].

PCOS Phenotypes through Life Cycle

The development of PCOS has been associated with a sequence of events affecting fetal life and the programming of endocrine axes, especially carbohydrate metabolism and adrenals secretion. Indeed, girls born small for gestational age or large for gestational age, this being an indirect index of exposure to stressful intrauterine conditions, manifest a high incidence of PCOS in adolescence. Furthermore, in girls with early adrenal androgen secretion clinically disclosed as premature pubarche, several components of PCOS have been found, such as insulin resistance and visceral adiposity, in comparison to their normal peers. In addition, an increased proportion of these girls develop PCOS in adolescence, indicating a common pathogenetic link between these two nosologic entities. Also most interestingly, girls born small for gestational age who develop premature adrenarche later on have a significantly higher tendency to develop full-blown PCOS in adulthood compared to other girls who express only one of these two conditions. This observation suggests that exposure of a female to harmful events during fetal life and the peripubertal period may considerably affect her metabolic, hormonal, and reproductive phenotype [6].

With regard to post-menopause, there are strong indications that exposure to numerous cardiovascular (CV) risk factors that have set in as from adolescence has a profound impact on mortality by multiplying post-menopause CV incidents. Although solid evidence is still lacking, available data point to higher rates of CV disease in women with a history of PCOS compared to age- and BMI-matched peers. However, it should be emphasized that these data were obtained from the evaluation of women strictly in accordance with the NIH criteria and not from those with PCOS diagnosis according to the Rotterdam criteria [7].

Common Problems with Respect to Criteria Used for PCOS Classification

Based on the currently used definitions, four different phenotypes have been established for PCOS classification, as illustrated in figure 1. It remains under investigation whether the spectrum of phenotypes reflects differences in the severity of the

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syndrome and its long-term complications. These issues have not as yet been clearly elucidated and conflicting data have been reported. The reason for this discordance is the heterogeneity of the syndrome, the different techniques applied in the several studies, and the lack of accuracy and reliability that is apparent in the evaluation of PCOS subjects. We will illustrate and underline these differences with the aim of constructing uniform diagnostic criteria for the diagnosis of PCOS within the range of the different phenotypes.

Androgens

Hyperandrogenemia constitutes one of the cardinal features of PCOS and, indeed, in a significant number of patients (60–80%) elevated circulating androgen levels have been disclosed. However, there are several basic points that the clinician should bear in mind regarding androgens and PCOS. First of all, circulating levels of androgens in women of reproductive age reflect both ovarian and adrenal production. Specifically, ovaries and adrenals contribute equally (50%) to total testosterone and androstenedione levels, whereas dehydroepiandrosterone sulfate (DHEAS) values are almost exclusively produced by the adrenals. This information is of basic clinical importance since basal androgen measurement may directly guide diagnosis to an adrenal source of hyperandrogenemia. Nevertheless, age also affects androgen levels, data providing evidence that there is a gradual fall through time. Furthermore, it must be emphasized that androgenic activity is not similar for all androgens. Specifically, dehydroepiandrosterone exerts the lower biological action, whereas testosterone is the most potent circulating androgen in women.

An as yet unresolved issue with respect to hyperandrogenemia in PCOS is: which is the best method for androgen assessment and especially testosterone? The vast majority of assays have been designed for testosterone estimation in males in whom normal values are ten times higher than in women. This methodological problem is reflected in the great variation of testosterone values among different assays employed in females. Although equilibrium dialysis and tandem mass spectrometry are considered the gold standard for testosterone estimation, they are very expensive and are limited to a certain number of laboratories, this making their use inappropriate on clinical basis. Since RIAs are not appropriate for measuring androgens in women due to their low diagnostic yield, immunoassay after extraction and chromatography is preferred as a more practicable and cheaper solution. However, the lack of an assay designed for the low testosterone concentrations found in women is a major limitation. To overcome this difficulty, the lab needs to introduce its own normal standards, also given the fact that there are national and regional differences of testosterone levels among different populations.

Another ongoing debate is whether total or free testosterone (FT) should be evaluated. It must be underlined that only 1–2% of testosterone circulates in its free and

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biologically active form, while the rest is bound tightly to SHBG (65%) and weakly to albumin (33%). Consequently, alteration of albumin levels or the existence of any factor modifying SHBG will affect total testosterone levels. Hyperinsulinemia and obesity, two common factors in PCOS, will decrease SHBG, and glucocorticoids and growth hormone exert the same effect. By contrast, thyroxine and estrogen will increase SHBG, this being one of the mechanisms of the therapeutic effects of oral contraceptives in PCOS. In order to overcome this difficulty, the use of the ratio of total testosterone to SHBG, namely the 'free androgen index' or FAI (FAI: the ratio of total testosterone to SHBG multiplied by 100), has been introduced as an index of bioavailable testosterone. However, this index has not been widely accepted as yet on clinical grounds, although several studies have shown a better correlation with PCOS features than total or FT values.

Nevertheless, the Androgen Excess Society and Endocrine Society have suggested that the measurement of FT concentration using high-quality and sensitive assays is the most useful test to detect hyperandrogenemia in PCOS. FT circulating levels reflect both the degree of ovarian and adrenal testosterone production as well as the proportion of testosterone bound to SHBG. Accordingly, in PCOS where androgen excess and inhibited SHBG hepatic production coexist, FT concentrations can be found elevated, even in the cases of patients with total testosterone levels in the normal range. In fact, several studies have found hyperandrogenemia with FT evaluation in about 60% of women with PCOS, whereas the analogous values for total testosterone were less than 50% [8].

The issue of which other androgens should be evaluated is still a matter of debate. There are data obtained from large studies showing that in about 30% of PCOS, only androstenedione levels are elevated and, furthermore, that these women exhibit a more 'severe' form of PCOS as regards metabolic profile. In addition, in 10% of women with PCOS only DHEAS levels are elevated, and in these cases a thorough evaluation via Synacthen test and even CYP21 genotyping is needed to exclude non-classical congenital adrenal hyperplasia (NC-CAH). However, the combined measurement of FT, total testosterone, and DHEAS has a higher sensitivity of 75% in distinguishing hyperandrogenemia in women with PCOS, versus normal population.

Another aspect that should be discussed is the impact of the specific day of menstrual cycle when blood sampling is carried out on androgens values. In general, the recommendation is that androgens be evaluated during the ovulatory phase, and especially on the first 3–5 days of menstruation, given that a 20–30% rise in both total and free testosterone takes place prior to the LH surge, namely between the 7th and 10th day of a normal ovulatory circle. Since many women visit their doctors during amenorrheic or oligomenorrheic periods, it is not easy to assess androgen levels that can best be measured during spontaneous menstruation.

Many clinicians thus suggest the induction of withdrawal bleeding with the use of progesterone with the aim of overcoming this difficulty. However, as our group

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has recently shown, it is far more useful to evaluate progesterone levels and, if they are suggestive of anovulation (levels <3 ng/ml) [9.54 nmol/l] to proceed the next day to androgen evaluation. The results obtained with this technique are similar to those obtained with the induction of withdrawal bleeding, enabling the assessment of androgens in a faster and much more effective way [9]. Finally, we should keep in mind that a spontaneous ovulation is capable of restoring androgen levels to normal range in a woman with PCOS despite the fact that hyperandrogenemia has been identified during anovulatory cycles.

In conclusion, although hyperandrogenemia is a sine qua non in PCOS diagnosis, there are still plenty of questions which have not been answered yet, namely: (a) which androgen(s) should be measured; (b) how often; (c) which are the normal androgen levels in women, and (d) which analytical techniques should be employed.

Hirsutism

Hirsutism is defined as excessive terminal hair growth that takes on a male pattern distribution. In order to better understand the phenomenon of hirsutism, some background information is needed. Hairs cover the entire surface of the human body, with the exception of the lips, palms of the hands, and soles of the feet. Hair type can be subdivided into three categories, asexual, ambo-sexual and sexual, depending on the effects of androgens. Asexual hair is localized in the eyebrows, the eyelashes, and the lateral and occipital scalp and is insensitive to androgens levels, whereas ambo-sexual hair is restricted to the pubis and axilla as well as the lower arms and legs, and is sensitive to low androgens levels. Sexual hair is that found on the chin, face, chest, abdomen, back, thighs, and upper arms, with high levels of circulating androgens being needed to generate its production. Accordingly, in PCOS the detection of increased hair in these areas, which is termed hirsutism, is suggestive of hyperandrogenism.

Although hirsutism constitutes the most common clinical manifestation of hyperandrogenism (60–70%) in women with PCOS, the estimation of its degree is still controversial. Several methods exist for the objective assessment of hair growth, such as the weighing of the hairs, the measurement of the outer diameter of either plucked or clipped hairs, the determination of hair density or the 'vellus index', etc. However, these techniques are costly and time-consuming and are, on the whole, not widely employed in the evaluation of PCOS. In contrast, in clinical practice excessive hair growth in women is generally quantified with the use of the Ferriman-Gallwey scoring system (FG). This system grades terminal hair growth on a scale from 0 to 4 on eleven anatomical sites and uses the sum of nine areas to generate an overall hirsutism score. Scores of ≥8 or ≥5 have been commonly accepted as abnormal, but this system has several disadvantages. It is highly subjective, and studies have shown as much as a 10-point variation between researchers evaluating the same patient.

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Furthermore, as the FG score reflects the total score, hair growth on arms or legs is considered equivalent to hair growth on the face or chest, although these areas reflect different sensitivity to androgens, as explained above. In addition, age and ethnicity significantly influence hair growth due to variances in 5 α-reductase activity, so that different normal values should be expected among different populations and age groups, although precise determination of these has not as yet been established. Finally, the evaluation of certain areas (e.g. chest, thighs) causes discomfort in the patients, especially in the case of a woman being examined by a male examiner. Recently, a modified FG score was tried out assessing only chin and abdomen. This showed a good correlation with the total FG score and gave indication of being a promising approach, although it requires further verification from other research groups [10].

Anovulation

In 1990, the anovulatory process was pinpointed as being a chief manifestation of PCOS. Menstrual irregularity in women with PCOS occurs due to anovulation, and menstrual disturbances usually present in the form of oligo-amenorrhea (fewer than six to eight episodes of menstrual bleeding per year or menses that occur at intervals greater than 35 days). The medical definition of chronic anovulation in PCOS is based: (a) on the exclusion of other causes of anovulation (e.g. hyperprolactinemia, hypothyroidism, etc.), and (b) on the measurement of progesterone values 8–12 days prior to menstrual bleeding and/or the absence of corpus luteum determined through ultrasonography, for three consecutive cycles. Ovulation is confirmed when serum progesterone measurements are greater than 5 ng/ml [10 nmol/l]. However, inappropriate timing of progesterone measurements will obviously lead to an inaccurate diagnosis of anovulation, progesterone measurement not being, in any case, the common practice.

In a significant percentage of studies, women who reported less than ten menstrual cycles per year were considered as anovulatory. The limitation of this commonly used approach is that it yields a large number of false positive and false negative results in PCOS study groups. False negatives are considered to be those women with more than 10 cycles per year, but who could be anovulatory, especially in the case of frequent menstruation; false positive women include those with 8 cycles, but all ovulatory. Furthermore, ovulatory dysfunction may be present in women with PCOS who report regular menstrual cycles. Accordingly, menstrual history alone is insufficient for definition of PCOS phenotypes in women whose cycles are regular, especially in the presence of hyperandrogenism. In the event of doubt, progesterone evaluation should be carried out.

It should also be borne in mind that in a normally ovulating woman, the loss of one to two ovulations per year is considered a natural phenomenon. Moreover,

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central obesity and insulin resistance are strongly associated with anovulation and a transition between anovulation and ovulation has been documented in women with PCOS undergoing caloric reduction programs leading to relatively rapid weight loss. It is hence possible that a woman considered to be anovulatory may ovulate after a 5–10% loss of BMI, this being a situation that the clinician should always take into consideration for both diagnostic and therapeutic reasons [11].

Polycystic Ovarian Morphology

As shown in table 1, confirmation of the existence of polycystic ovaries requires either the visualization of 12 or more follicles measuring 2–9 mm or ovarian volume bigger than 10 cm^3. Both situations are suggestive of PCOM even if they are detected in the one ovary. This definition is more useful than the previous one, whereby the assessment of stromal echogenicity and/or follicle distribution pattern were necessary characteristics that have been abandoned due to their high degree of subjectivity.

However, ovarian volume and, in particular, follicle measurement is a subjective process highly dependent on the accuracy, experience, and attentiveness of the ultrasonographer. In an interesting study conducted by Amer's group, it was found that an agreement for PCOM between observers was found in only 50% of cases. It must be underlined that the cutoff value of 12 follicles was found to have increased specificity (99%) and sensitivity (75%) for PCOM in only one study. Other studies have not reproduced these findings, increasing the noise of ultrasonography use in PCOS diagnosis. For example, in a large study of more than 600 women with PCOS and 100 controls, 12 follicles per ovary were found in about half of controls. As a consequence, among gynecologists PCOM is a very strong factor for PCOS diagnosis, whereas according to endocrinologists it constitutes a supportive but not a definitive tool for diagnosis. Furthermore, several reproductive endocrinologists suggest different criteria in clinical practice, such as >20 follicles per ovary or increased stroma/total area ratio, whereas medical imaging specialists use older criteria (stroma/follicles pattern) because of their long familiarization with them.

Furthermore, since follicles number and ovarian volume are highly correlated with the current use of oral contraceptives (OCPs), an interval of 3 months after OCP discontinuation is the minimum time needed before ovarian ultrasonography is carried out. Similar actions in ovarian morphology should be expected in the case of metformin administration and, to a lesser degree, with antiandrogen treatment.

Another factor that affects ovarian morphology is age. About 20% of women of reproductive age display PCOM without any other sign of PCOS (hyperandrogenism and anovulation), this fraction being still higher in adolescents among whom 40–50% of girls display PCOM, which, however, resolves through years. Finally, we should keep in mind that a spontaneous ovulation is sufficient to totally correct ovarian morphology, especially follicle number. In order to ensure the best quality of ultrasound in

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