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Polycystic ovary syndrome - Phenotypes and diagnosis

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ORIGINAL ARTICLE

Polycystic ovary syndrome – Phenotypes and diagnosis

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Abstract

Polycystic ovary syndrome (PCOS) is a heterogeneous spectrum of symptoms lasting throughout the lifecycle. The syndrome combines reproductive as well as metabolic aberrations associated with increased cardiovascular risk. The presence of three different definitions for the diagnosis of PCOS reflects the phenotypic diversity of the syndrome. The clinical manifestations and the sequelae of PCOS vary throughout the lifecycle, partly depending on environmental factors which may affect the integral components of the syndrome, namely ovarian steroidogenesis, ovulation and insulin resistance. As the patient grows older, particularly in the postmenopausal period, the cardiovascular risk profile may translate into increased rates of cardiovascular morbidity.

Key Words: *Polycystic ovary syndrome, phenotypes, lifecycle*

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Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrinopathy of women of reproductive age [1]. Although it is widespread, the variability of clinical presentations and the complexity of its etiopathogenesis make PCOS a difficult diagnosis to place in everyday clinical practice.

More specifically, women with PCOS display hyperandrogenemia, insulin resistance and chronic anovulation, as well as central adiposity with dysfunctional adipose tissue [2]. All these features may be present to different degrees and various combinations, thus leading to a wide spectrum of phenotypes [3]. Moreover, PCOS affects women from early prepubertal years to postmenopausal period and its manifestations are changing throughout the lifecycle [4]. Due to this phenotypic variety the definition of PCOS has been a matter of constant debate as reflected by the presence of three different diagnostic definitions [5–7].

The phenotype of the syndrome may be significantly influenced by environmental factors, like overnutrition leading to obesity [2,8,9]. Obese patients appear to have a more adverse phenotype in reproductive and metabolic terms. More specifically, obesity is associated with a greater degree of insulin resistance and hyperinsulinemia as well as a greater mass of central adipose tissue with impaired function. Insulin resistance and dysfunctional adipose tissue appear to contribute to worsening of hyperandrogenemia and anovulation in the setting of PCOS [2].

Additionally, accumulating data suggests an additional role of diet, beyond overnutrition and obesity [9]. In particular, advanced glycated end products (AGEs), a wide class of molecules, which are partly derived from diet and partly endogenously produced, may participate in the pathogenesis of PCOS [9,10]. These molecules were found to be increased in women with PCOS, independent of other metabolic parameters [11].

Definitions and phenotypes

In 1990 the first formal attempt to define PCOS resulted in the classic definition of PCOS by the National Institute of Child Health and Human Development. This definition requires the combined presence of anovulation and biochemical or clinical hyperandrogenism [5].

Although the ultrasonographic finding of polycystic ovarian morphology may be present in about

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20–30 % of normally ovulating, not hyperandrogenemic women, a significant portion of physicians still consider this criterion as mandatory for the diagnosis of PCOS [12]. In that context, the National Institutes of Health (NIH) criteria were revised during the 2003 Rotterdam meeting, where the occurrence of polycystic ovaries was added to the diagnostic criteria, along with the statement that patients needed to score positive for only two out of three criteria [6]. The ultrasonographic diagnosis of polycystic ovaries requires the visualization of 12 or more follicles measuring 2–9 mm or the presence of at least one ovary larger than 10 cm^3. Both situations are suggestive of polycystic morphology (PCOM) if they are detected in at least one ovary [13]. Using the possible combinations of the Rotterdam criteria, four different phenotypes of PCOS are identified:

- hyperandrogenism (clinical or biochemical) plus chronic anovulation [H-CA];
- hyperandrogenism plus polycystic ovaries but with ovulatory cycles [H-PCO];
- chronic anovulation plus polycystic ovaries without clinical hyperandrogenism [CA-PCO] and finally,
- the triad of hyperandrogenism, chronic anovulation, and polycystic ovaries [H-CA-PCO] [6,14].

The Rotterdam criteria do not consider any of the major features of PCOS as mandatory for the diagnosis, since they identify polycystic morphology, chronic anovulation and hyperandrogenism as being equivalent diagnostic criteria [6]. The Rotterdam criteria imply that PCOS may manifest as a spectrum of symptoms and may be diagnosed in the absence of androgen excess. However, many experts in the field questioned this thesis and in 2009 the Androgen Excess & PCOS (AE-PCOS) Society charged a Task Force to review all available data and recommend an evidence-based definition [7]. The new AE-PCOS Society definition highlighted that PCOS is principally a hyperandrogenic disorder and that hyperandrogenism comprises a *sine qua non* for the diagnosis of the syndrome. The second criterion required for PCOS diagnosis according to the AE-PCOS society is either anovulation or polycystic ovarian morphology [7]. Overall, regardless of the definition applied, PCOS is a diagnosis of exclusion, since other androgenic entities should be ruled out in order to place the diagnosis of the syndrome [5–7].

PCOS phenotypes throughout the life cycle

The development of PCOS may start from intrauterine life involving the programming of endocrine axes, namely the hypothalamic-pituitary-ovarian and adrenal axis as well as the pathways of carbohydrate metabolism. More specifically, girls born small for gestational age (SGA), possibly exposed to an abnormal intrauterine environment, may carry an increased risk of developing PCOS in adolescence [15]. Furthermore, girls with premature pubarche and adrenarche, defined as the presence of increased adrenal androgen secretion earlier than the eighth year of age, may display several components of PCOS, like insulin resistance and visceral adiposity. In addition, an increased proportion of these girls will develop the full-blown syndrome in adolescence, suggesting a common pathogenic link between PCOS and premature adrenarche [15]. Hence, low birth weight and premature pubarche/adrenarche appear to be possible precursors or predisposing conditions for the development of PCOS. Most interestingly, girls who combine a history of low birth weight and a history of premature adrenarche have a higher tendency to develop PCOS in adulthood compared to those girls who have only one of the two predisposing conditions [15]. This observation suggests that early events during fetal life, prepuberty and the peripubertal period may be major determinants of the female's metabolic and reproductive phenotype.

The adverse metabolic phenotype of PCOS encompasses a constellation of cardiovascular risk factors. The presence of these factors from the prepubertal period and their lifelong persistence may have a profound impact on cardiovascular morbidity and mortality. Although robust data are still lacking, some relevant studies have suggested a higher rate of cardiovascular disease in women with a history of PCOS compared to age- and BMI-matched controls [16]. However, it should be emphasized that these data appear to apply only to the classic form of PCOS fulfilling the NIH criteria and cannot be extrapolated to the broader spectrum of PCOS as defined by the Rotterdam criteria [16].

Prevalence of PCOS by different diagnostic criteria and common concerns regarding the classification of PCOS phenotypes

PCOS is 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 available studies as well as study design limitations. Nevertheless, the PCOS prevalence is estimated to be 6.5 % according to the NIH criteria in women of Caucasian origin [1]. The implementation of the newer criteria increases the prevalence to 15–25 % and 6–15 % according to the Rotterdam and the AE-POS Society recommendations, respectively [14,17]. Regardless of the criteria used, it is clear that PCOS comprises a major concern for the clinician and a common health problem for young, otherwise healthy women.

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Based on the currently used definitions, the spectrum of PCOS includes four different phenotypes. It remains under investigation whether these phenotypes reflect differences in the severity of the syndrome and its long-term complications and these issues have not as yet been clearly elucidated. The reason for this discordance is the heterogeneity of the syndrome as well as methodological issues. In particular, the inconsistent methodology between studies and the lack of reliable assays for the measurement of serum androgens in women are major limitations in the precise identification of PCOS phenotypes and the quantification of hyperandrogenemia in women with PCOS [18].

Most androgen assays have been designed for the measurement of serum testosterone in males in whom normal values are ten times higher than in women. This methodological problem accounts for the great inter-assay variation of testosterone values in women (testosterone concentration measurements by different assays in the same woman). Although equilibrium dialysis and mass spectrometry are considered the gold standard, the measurement of testosterone by these methods is laborious and expensive and thus, inappropriate in the clinical setting. Since radioimmunoassays (RIAs) are not appropriate for measuring androgens in women due to their low diagnostic yield, the immunoassay after extraction and chromatography is the preferred solution having low cost and easier application. However, the lack of an assay designed for the low testosterone range in women is a major limitation. To overcome this difficulty, the laboratory should establish its own reference intervals of testosterone taking into account all the appropriate variables, e.g. age, race, time of the day, etc. [18].

Another ongoing debate is whether total or free testosterone (FT) is the most appropriate measure to evaluate androgen excess in women. Considering that only 1–2 % of testosterone circulates in its free bioactive form and the rest is bound tightly to sex hormone binding globulin (SHBG) and weakly to albumin, any factor modifying either of these binding proteins will affect total testosterone concentrations [18].

Nevertheless, the Androgen Excess Society and the Endocrine Society recommend that the measurement of FT concentration using high quality and sensitive assays is the most useful index to detect hyperandrogenemia in PCOS [7]. Circulating concentrations of FT reflect both the degree of ovarian and adrenal testosterone production as well as the proportion of testosterone bound to SHBG. Considering that PCOS combines androgen excess and inhibition of hepatic SHBG production of SHBG, FT concentrations can be found elevated, even when total testosterone concentrations remain within the reference interval [7].

Overall, although hyperandrogenemia is recognized as a major component of the diagnosis of PCOS, several issues remain unresolved. The most important issues are:

(1) which androgens should be measured and how often,
(2) what is the reference interval for androgen concentrations in women, and
(3) which analytical techniques should be employed [7,18].

Another major issue related to the diagnosis of PCOS by Rotterdam criteria involves the ultrasonographic diagnosis of polycystic ovaries. More specifically, the measurement of the ovarian volume and the follicle number is a subjective process depending on the expertise and the experience of the ultrasonographer. Additionally, polycystic ovaries are present in a significant portion of reproductively healthy adolescents and women. In particular, 40–50 % of adolescent girls display polycystic ovarian morphology which resolves through years but still persists in 20 % of adult women throughout their reproductive years. In conclusion, the ultrasonographic characterization of polycystic ovaries requires a detailed report by an experienced ultrasonographer recording the number and the distribution of follicles as well as the ovarian volume. Even when this prerequisite is fulfilled, polycystic ovarian morphology is not sufficient to place the diagnosis of PCOS [7].

The introduction of the new PCOS phenotypes by Rotterdam criteria generated debate regarding the long-term sequelae of PCOS in the broad phenotypic spectrum of the syndrome. The classic PCOS phenotype as defined by the NIH criteria appears to display an unfavorable hormonal and metabolic profile associated with a clustering of cardiovascular risk factors, including disorders of glucose tolerance, dyslipidemia and subclinical inflammation [3,19–21]. Furthermore, Shaw and colleagues have reported that postmenopausal women with classic PCOS features (hypeandrogenism & chronic anovulation) display a higher rate of cardiovascular (CV) morbidity and mortality [16]. A striking finding of this study was that CV morbidity/mortality was not increased in women with a history of isolated hyperandrogenemia or isolated menstrual irregularities. Hence, only the classic PCOS seems to be associated with increased CV risk. This study highlighted the need for early identification of CV risk factors and close surveillance of patients with classic PCOS throughout life, focusing on cardiovascular health issues particularly after menopause [16].

Several studies have suggested that women with PCOS based on the NIH criteria exhibit a more adverse cardiometabolic profile compared to newer phenotypes [3,19–21]. This observation is only partly explained by the fact that women with classic PCOS tend to be more obese. In particular, the degree of dyslipidemia, central adiposity, insulin

resistance, and metabolic syndrome prevalence appears to be significantly higher in women with classic PCOS compared to women with non-classic PCOS, even when the groups were matched for age and BMI [3,19–21]. Moreover, available data suggest that oligoanovulatory patients with polycystic ovaries but without hyperandogenemia display mild endocrine abnormalities, but not the metabolic features of PCOS [3]. Similarly, a recent study from Turkey reported that the estimated CV risk and the degree of subclinical atherosclerosis assessed by the carotid intima thickness were lower in women with PCO and hyperandrogenemia than in the classic phenotype [20].

Overall, the cardiometabolic implications of the new, non-classic PCOS phenotypes remain under investigation. This issue is of utmost importance given that 25 % of PCOS patients diagnosed with the new criteria are evenly divided between ovulatory and nonhyperandrogenic PCOS phenotypes [22]. To elucidate this issue, longitudinal studies should follow-up women with PCOS stratified by phenotype and address the potential phenotypical changes and transition from one phenotype to the other. It can be postulated that women who have presented once with a mild phenotype may at a later stage of life develop a worse phenotype with the known adverse sequelae, depending on their exposure to environmental factors like weight increments. Such phenotypical changes may be critical to the long-term CV implications of PCOS and cannot be assessed by observational or retrospective studies.

Exploring the impact of nutrition on PCOS phenotypes: The potential role of advanced glycated end products (AGEs)

As discussed above, obesity is a recognized triggering and aggravating factor in the natural course of PCOS [9]. In this context, diet aiming at weight loss in obese patients and maintenance of ideal weight in lean patients appears to be a significant tool in the therapeutic management of PCOS [8]. Meanwhile, the quality of diet, particularly dietary AGEs which are found in large quantities in heat-treated foods, appear to have a detrimental role, independent of calorie intake and overnutrition [10]. More specifically, AGEs have been recognized as potent endocrine disruptors [23,24]. The term 'endocrine disruptor' designates any molecule found in the environment which may interfere with hormone biosynthesis, metabolism, or action, resulting in a deviation from normal homeostasis and/or reproduction. AGEs fulfil these principles since they exhibit strong oxidative, proinflammatory, and proatherogenic properties and have been associated with increased cardiovascular morbidity in both diabetic and non-diabetic subjects [23,24].

PCOS has been associated with increased circulating of AGEs, independently of age, obesity, insulin resistance and glucose intolerance. Additionally, serum AGEs concentrations were found to be higher in women with classic PCOS than in their counterparts with the new ovulating phenotype, despite the fact that age, BMI, and degree of insulin resiatnce was comparable between these groups [11]. On the other hand, in those with anovulation and polycystic ovarian morphology, AGEs levels were similar to controls [11,25].

Furthermore, AGEs appear to have a differential role in different PCOS phenotypes: Not only their serum concentrations are higher but also AGEs concentrations follow the same pattern as anti-Müllerian hormone, a specific marker of ovulatory dysfunction in PCOS [25]. On clinical grounds, these observations are in accordance with the observation that high AGEs concentration in follicular fluid and serum are correlated negatively with fertility rate [26]. These findings suggest that AGEs may interfere in the ovulatory process having a differential role in different PCOS phenotypes.

Conclusions

PCOS is a lifelong disease involving a continuum of clinical manifestations and a spectrum of different phenotypes. The actual impact of these phenotypes on cardiometabolic morbidities and mortality has not been elucidated as yet. At the time of diagnosis it is unknown whether a woman presenting with hyperandrogenism or anovulation and polycystic ovaries on ultrasound will develop the full-blown syndrome later in life. Therefore, a careful individualized approach is required to follow-up these women throughout their life. Most importantly, the clinician should not only address the problem which prompted the woman to seek medical assistance but also discuss the importance of lifestyle in avoiding the clinical exacerbation of the syndrome and its long-term health risks.

Questions and answers

Q (Lane): As a clinician, when you give metformin what are your outcome measures?
A (Diamanti): It depends. If you give it to a woman who has insulin resistance and anovulatory cycles, we may evaluate the normalization of the cycles but if a patient wants to conceive, metformin is not the first choice drug. Usually we start with clomiphene to normalize the ovulation. If the patient is resistant to clomiphene, adding metformin may help. The clinical treatment depends on the phenotype. Now metformin is used for the metabolic phenotype and as an adjuvant in the reproductive phenotype but it is not used in the hyper androgenic phenotype.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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