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REVIEW

PCOS phenotype focus: phenotype D under the magnifying glass

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Abstract
Polycystic ovary syndrome (PCOS) is defined as the combination of polycystic morphology, hyperandrogenism, and ovulatory disruption; this heterogeneity presents a conundrum for the medical community. The Rotterdam criteria have governed the diagnosis of PCOS, separating the patient cohort into four distinct phenotypes. It has been suggested that the lone normoandrogenic phenotype, so-called phenotype D, should not be classified as a PCOS subtype, with phenotypes A, B, and C displaying a hyperandrogenic biochemical and clinical profile thought to be characteristic of PCOS. To understand how to treat phenotype D patients, this review shines a spotlight on the phenotype, gathering various reports of how phenotype D is differentiated from the other PCOS phenotypes.

Keywords Polycystic ovary syndrome · PCOS phenotype D · Rotterdam criteria · PCOS phenotype prevalence · Hyperandrogenism · Assisted reproductive technology (ART)

Introduction

PCOS is described as the most common endocrinological disorder affecting women of reproductive age, and represents a worldwide health concern [1]. Patients with PCOS suffer from a myriad of health issues including reproductive, metabolic, and psychological disorders, in addition to an overall reduction in quality of life [2]. The initial attempt to standardize the definition of PCOS came in 1990 with the NIH criteria, which defined PCOS as a syndrome that presented hyperandrogenism (HA) and ovary dysfunction (OD) in the absence of secondary causes [3]. The NIH criteria were controversial at the time, as they did not include polycystic ovarian morphology (PCOM) as detected by ultrasound, a popular method of identifying PCOS at the time outside the US [4]. In 2003, a meeting of the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine in Rotterdam resulted in the Rotterdam criteria [5]. These criteria have been continuously updated and currently define PCOS as a syndrome that presents two out of three of the following [6, 7]:

(1) Biochemical and/or clinical HA
(2) Oligomenorrhea or amenorrhea (cycles > 35 days apart or < 8 cycles in a year)
(3) PCOM (≥20 follicles measuring 2–9 mm in diameter and/or an ovarian volume > 10 cm^3 in at least one ovary)

Their combination led to the description of four individual phenotypes A, B, C, and D described in Fig. 1.

In 2006, the Androgen Excess-PCOS Society (AE-PCOS) suggested an amendment to exclude phenotype D, the only normoandrogenic phenotype described by the Rotterdam criteria [8]. It was thought that HA was of vital importance to the diagnosis of PCOS and as such phenotype D should be considered as a separate condition. These criteria were never widely adopted and to date, the Rotterdam criteria are still used for diagnosis of the condition, governing patient recruitment and treatment. Unfer et al., among others, have argued for a separation between the hyperandrogenic phenotypes (A, B, and C) and phenotype D, with the opinion that they are likely two separate conditions with different

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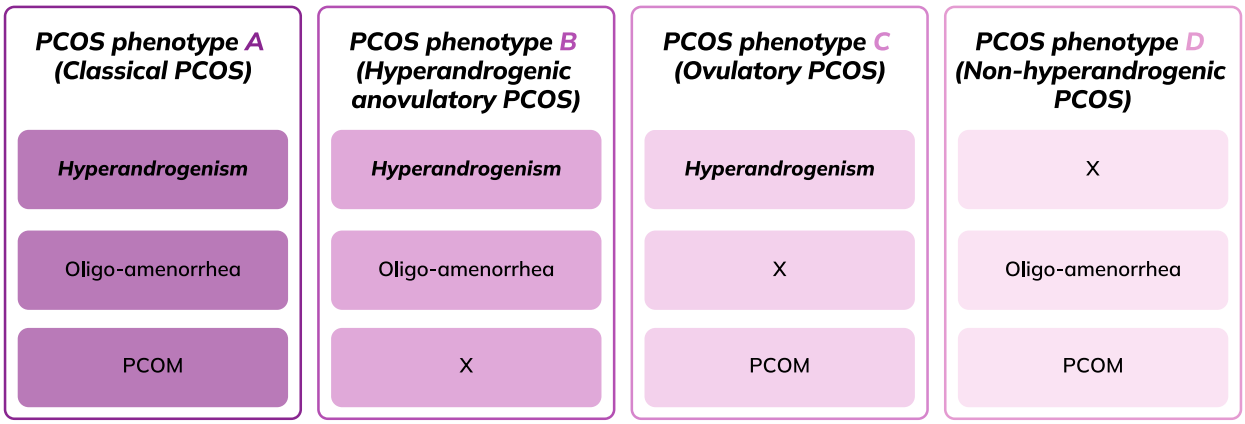

Fig. 1 Features of the four phenotypes as described by the Rotterdam criteria. *PCOM* polycystic ovary morphology

etiologies [9, 10]. This review focuses upon phenotype D, to build a characteristic profile of this fiercely debated phenotype.

Phenotype distribution—where is phenotype D most prevalent?

The phenotypic distribution of PCOS differs throughout the world. To investigate the spread of phenotypes, in Fig. 2, we selected example distributions from various studies conducted in literature. The literature search was performed with PubMed and Google Scholar between May–June 2023 using the search terms "PCOS", "PCOS phenotype", "Rotterdam criteria", "PCOS phenotype D", and "normoandrogenic PCOS". Studies conducted between 1998 and 2023, which recruited patients via application of the Rotterdam criteria and reported stratification of Rotterdam phenotype, were included. While the data are far from complete, trends can be observed. For example, phenotype D seems to be far more common in east Asia, particularly Vietnam and South Korea where over 65% of the sampled study population demonstrated phenotype D [11, 12]. More work is required to calculate an accurate worldwide distribution of the phenotypes, as the current research is overrepresented by Europe and Asia, with relatively few clinical trials having been

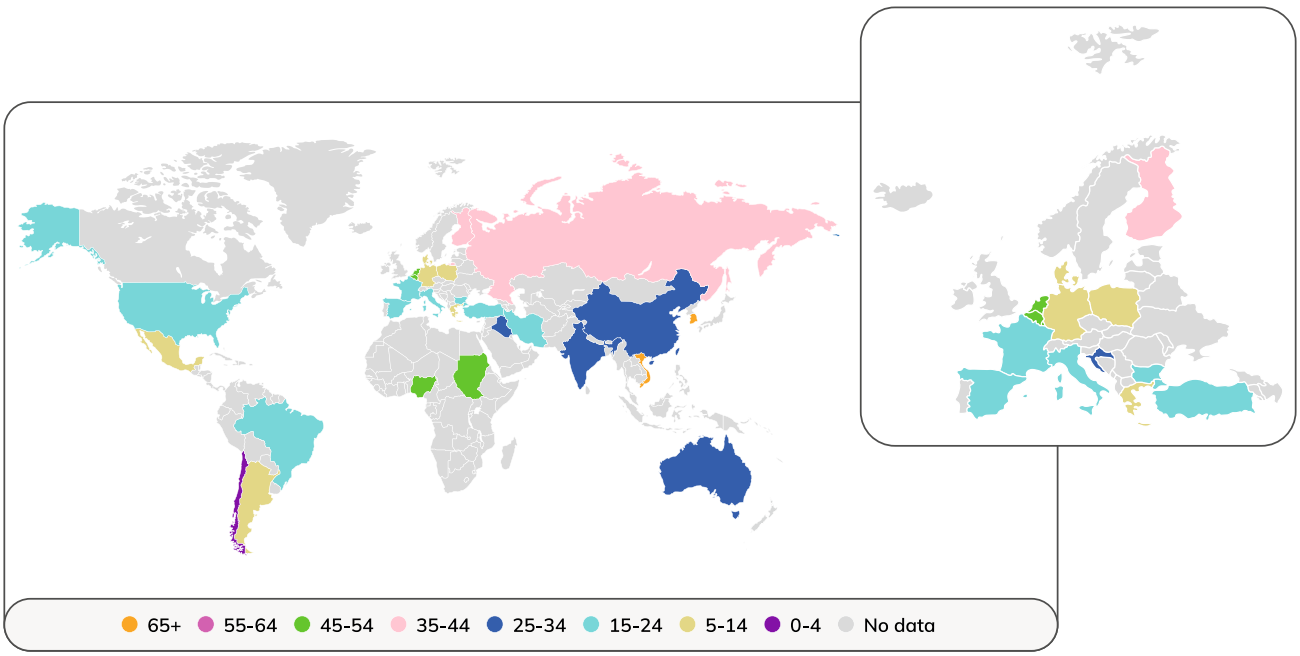

Fig. 2 Worldwide prevalence of phenotype D, numbers listed as percentages, a full list of accompanying studies can be viewed online within the supplementary material

performed in Africa. In addition, application of the Rotterdam criteria is not uniform across all countries, complicating population sampling. Furthermore, PCOS phenotype is not reliably reported in patient recruitment, this is reflected in the types of clinical trials routinely performed in the US. In a search using the keyword "PCOS" for studies based in the US, of the 296 studies, no trials reported differentiation of patient phenotype (Clinicaltrials.gov) [13]. Furthermore, as phenotype D does not present visibly identifiable clinical HA (hirsutism, acne, and alopecia), it is possible that phenotype D is underdiagnosed in respect to other phenotypes [14]. Therefore, it is evident that a greater number of population studies worldwide are required to properly map phenotype prevalence and to explore potential explanations for the observed regional distribution of PCOS phenotypes.

Patient profile of a "typical" phenotype D patient

Hormonal profile

Profiling the PCOS phenotypes is hindered by conflicting data from clinical studies, caused by variable sampling techniques and sizes, patient recruitment, in addition to the age, ethnicity, and fertility state of the sampled patients. To establish a hormonal profile of PCOS phenotype D, numerous studies have reported on the LH/FSH ratio in phenotype D. Several authors have observed an elevated LH/FSH ratio vs control populations [15, 16], while others describe an LH/FSH ratio more in line with healthy populations [17, 18]. Women with PCOS phenotype D are characterized by a reduced level of total testosterone compared to hyperandrogenic phenotypes [19]. This is occasionally accompanied by low androstenedione, free androgen index (FAI), and free testosterone [20–23]. However, not all androgens show the same trend, as DHEAS for example, demonstrates no significant change between phenotypes. In addition, SHBG, typically suppressed in the hyperandrogenic phenotypes, falls within healthy levels in phenotype D patients and is, thus, typically elevated in comparison to hyperandrogenic phenotypes [24]. As a consequence of phenotype D patients being normoandrogenic, these patients do not present clinical HA such as hirsutism and display a modified Ferriman–Gallway (MFG) score in the normal range [11]. Furthermore, phenotype D patients routinely have reduced levels of acne and alopecia in comparison to phenotypes A, B, and C [16].

Metabolic irregularities

The metabolic angle of PCOS has been extensively studied, with links to hyperinsulinemia, insulin resistance (IR), and metabolic syndrome (MS) being reported in literature [25, 26]. The apparent association between PCOS and metabolic disturbances has led associations such as the EGOI to suggest that metabolic indicators such as IR should be included in the diagnostic criteria [9, 27]. This is particularly true for phenotypes A, B, and C where there appears to be a link between the HA and metabolic irregularities. In this context, Zhao et al. reported significantly higher IR measured by the homeostasis model assessment-estimated insulin resistance (HOMA-IR) in the hyperandrogenic PCOS phenotypes vs phenotype D, the latter of which had similar levels to the control group [15]. In support of this notion, Tripathi et al. studied the prevalence of MS in the PCOS phenotypes, with phenotype D showing the lowest levels [28]. Nevertheless, the data regarding IR and MS are far from conclusive and should not be considered indicative of the entire syndrome. Stronger evidence has associated phenotype D with leaner patients with reduced waist–hip ratios [15, 29]. Some studies go further to report an average lower BMI; however, these studies are in the minority [30, 31].

In addition, significantly higher cholesterol, LDL, and triglyceride levels have been observed in phenotype A in comparison to phenotype D, supporting the link between the hyperandrogenic phenotypes and metabolic comorbidities such as hyperinsulinemia and obesity [32]. Furthermore, in the same study, lower HDL cholesterol levels were seen in phenotype B in comparison to phenotype D. This was supported by a study by Dadachanji et al. where reduced total cholesterol, LDL, triglyceride levels, and ApoB:ApoA-1 ratio were observed in patients with phenotype D in comparison to phenotype A [33]. However, many other studies have not reported a significant difference in cholesterol levels [21, 34]; therefore, while this may hint at a possible characteristic of the normoandrogenic phenotype, it should not be considered characteristic of phenotype D.

Phenotype D and hypothyroidism

Similarities can be observed between PCOS and hypothyroidism, whereby patients with hypothyroidism may present with menstrual disorders, HA, weight gain, dyslipidemia, and IR [35, 36]. A noteworthy difference in TSH levels can be seen in phenotype D, with patients demonstrating significantly lower levels than phenotype A and B [12]. A similar phenomenon has been observed in a community-based study investigating the prevalence of metabolic disorders across PCOS phenotypes in south western Iran, whereby PCOS phenotype D demonstrated significantly less TSH compared to hyperandrogenic PCOS [37]. To date, the cause of the fluctuation in TSH levels between the PCOS phenotypes has not been found; however, the metabolic involvement of HA in PCOS patients could provide a possible explanation and would be a fascinating topic for further study.

Phenotype D and psoriasis

PCOS and psoriasis are both commonly associated with IR, type 2 diabetes, obesity, and cardiovascular issues [38]. Furthermore, the incidence of PCOS in people with psoriasis is 47% more common than healthy populations, and women with PCOS commonly experience more severe symptoms of psoriasis vs control groups [39]. In a study by Moro et al., phenotype D PCOS patients showed the highest severity in Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA) scores in comparison to the other PCOS phenotypes and the control. It is suggested by the authors that more severe psoriasis is caused by inflammation, which is typically associated with anovulation, as all three anovulation phenotypes (A, B, and D) were poor performing regarding psoriasis markers in comparison to phenotype C [40].

Phenotype D and fertility

Fertility issues are unfortunately common in PCOS patients, as such the selection of the correct therapy choice is paramount to address the needs of patient. With this in mind, the effect that the PCOS phenotypes have on fertility care should be considered when advising patients with PCOS seeking pregnancy. In a study comparing outcomes after fertility treatment across phenotypes, it was found the combination of OD and PCOM (phenotypes A and D) resulted in a higher probability of adverse pregnancy outcomes. Specifically, incidences of ectopic pregnancy, miscarriage, and premature pregnancy were significantly increased in comparison to the control group [41]. This is not uniformly reported across all studies, as De Vos et al. reported that hyperandrogenic patients had a significantly worse outcome following in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI), than those without HA [live birth rate (LBR) phenotype A 25.8 vs 48% phenotype D] [42]. The presence of HA results in the growth of better quality embryos; therefore, phenotype D tends to be poor performing in this regard as seen in a study by Selçuk et al., whereby a significant decrease in embryo quality was seen in phenotype D (1.46 ± 1.18) vs phenotype B (3.76 ± 2.71) [43]. However, this did not correlate with an improvement in the number of embryos successfully transferred (phenotype B 1.21 ± 0.41 vs phenotype D 1.18 ± 0.44), suggesting that while HA may be correlated with improved embryo growth, it may cause issues in implantation [44]. One potential explanation for this is a reduction in endometrial quality, as HA as elevated androgens, together with elevated progesterone, may impair endometrial receptivity [44, 45]. Of note, this study did not include phenotype A patients which presents a major limitation to this study.

In vitro maturation (IVM) represents an alternative to conventional assisted reproductive technology (ART) for women with PCOS and was initially used to avoid the need of ovarian stimulation and the risk of ovarian hyperstimulation syndrome. However, this has become less relevant with the advent of gonadotrophin-releasing hormone agonist protocols [46, 47]. IVM remains an option for women with a high antral follicle count, specifically those with PCOS, where higher pregnancy rates have been seen vs their IVF counterparts [48]. In a study by Mackens et al., PCOS phenotype A patients formed significantly higher cumulus-oocyte complexes and matured oocytes in comparison to phenotype D; however, this did not result in an eventual improvement in maturation rate and fertilization rate [30]. The IVM data, therefore, mirror the IVF data where initial promise in the hyperandrogenic phenotypes does not correlate with an overall improvement in pregnancy outcome over phenotype D.

Clomiphene is a routinely prescribed therapy to induce ovulation in women suffering from fertility problems, including those with PCOS [49]. Response rates to clomiphene differ; therefore, to further understand how this effects PCOS patients, Sachdeva et al. investigated clomiphene response rates across the four PCOS phenotypes [50]. Phenotype A patients were the most resistant to clomiphene treatment (64.86%), while phenotype D demonstrated significantly lower levels of clomiphene resistance (16.67%), with similar observations having been reported in other studies [51, 52]. These results clearly differentiate the hyperandrogenic phenotypes and phenotype D, suggesting a correlation between HA and clomiphene resistance; however, the underlying cause of this correlation is unknown.

In recent years, the aromatase inhibitor letrozole has become preferred over clomiphene for the treatment of infertile PCOS patients [53]. Unfortunately, there is a relative paucity of literature regarding PCOS phenotypes and their response rate to letrozole. To the best of our knowledge, only a singular study conducted by Khurana et al. investigated the ovarian response to letrozole across the different PCOS phenotypes, whereby no significant difference was observed in response to letrozole therapy [20].

Concluding remarks

Since its inception, PCOS phenotype D has remained controversial, as it is considered as a separate condition by some members of the PCOS community. To facilitate the discussion around this phenotype, we have investigated the global prevalence of the phenotype and the hallmarks of phenotype D (Fig. 3). The studies around phenotype D are still somewhat limited; however, it is hoped that this review may spur

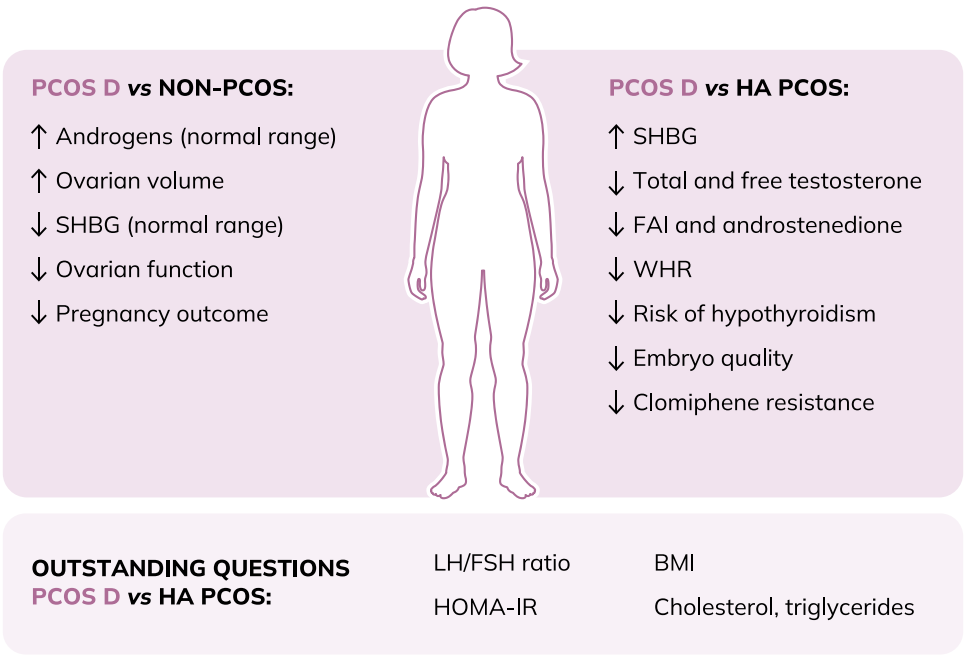

Fig. 3 Characteristics for phenotype D vs control and hyperandrogenic PCOS populations. The arrows denote an increase or decrease over the compared group. When the value is higher or lower than the healthy mean but does not reach clinical levels, this is specified as "normal range". The outstanding questions section specifies the indices for which it is not certain how they change between phenotype D and the hyperandrogenic PCOS subtypes. *BMI* body mass index, *FAI* free androgen index, *FSH* follicle stimulating hormone, *HA* hyperandrogenic, *HOMA-IR* homeostasis model assessment-estimated insulin resistance, *LH* luteinizing hormone, *PCOS* polycystic ovary syndrome, *SHBG* sex hormone-binding globulin, *WHR* waist–hip ratio

further investigation into the underlying mechanisms and possible therapies for PCOS phenotype D patients.

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Declarations

Conflict of interest SHM and VU are employed at Lo.Li. Pharma Srl, Rome (Italy).

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