Trends in
Endocrinology & Metabolism

CellPress

Opinion

Questioning PCOS phenotypes for reclassification and tailored therapy

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Precise diagnoses are essential for defining appropriate treatments. This is particularly true for polycystic ovary syndrome (PCOS), whose phenotypical manifestations have recently suggested a possible diversity of etiological factors. PCOS is defined on the basis of gynecological and endocrinological alterations, but the patients often display considerable metabolic impairments, such as insulin resistance, that may worsen typical symptoms. The Rotterdam criteria fail to address this aspect, and the medical community has recently started to consider them as misleading diagnostic tools, casting doubts on whether the term PCOS is suited to describe all the clinical manifestations observed. This Opinion collects and critically discusses the scientific reports that question the definition of PCOS, calling for a revision of the current diagnostic criteria.

Highlights

PCOS is routinely assessed using the Rotterdam criteria, which consider hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. These criteria have faced criticism in recent years.

These criteria yield four distinct phenotypes, three of which (A, B, and C) demonstrate hyperandrogenism, whilst the fourth, Phenotype D, does not. It is questioned whether they share the same etiopathogenesis, and whether alterations in insulin-like growth factor 1 or gonadotrophin levels could be responsible for Phenotype D.

Phenotypes A, B, and C seem to be associated with insulin resistance, especially as it pertains to hyperandrogenism, while this is less likely with Phenotype D. It has been suggested that this finding could trigger a reclassification of the PCOS criteria.

Tailored therapies are required, as a lack of specific treatments exist for phenotype D.

Alterations in PCOS diagnostic criteria over time

PCOS (see Glossary) remains at the forefront of medical research, being the most prominent endocrine disorder affecting 6–10 % of women of reproductive age [1]. Women living with PCOS are at an increased risk of numerous reproductive, metabolic, oncological, and psychological disorders, impairing their quality of life, and also that of any potential offspring [2]. The financial burden on the medical industry should also be considered, with PCOS treatments estimated to cost $4.3 billion in 2020 in the US alone [3]. Treatment of PCOS has proved challenging because of patients presenting with a variety of different ovarian and endocrinological issues, resulting in a series of phenotypic presentations.

In 1990, the National Institutes of Health criteria defined PCOS as a syndrome that presents clinical or biochemical evidence of **hyperandrogenism (HA)** and **ovulatory dysfunction (OD)**, with the exclusion of secondary causes [4]. Notably, the existence of **polycystic ovarian morphology (PCOM)** was not included at this point, as it can present in patients with neither anovulation nor signs of HA. The classification of PCOS was updated in 2003 at the European Society for Human Reproduction and Embryology and the American Society meeting in Rotterdam, which resulted in the revised Rotterdam diagnostic criteria incorporating the presence of PCOM presenting classically as a 'string of pearls' in an ultrasound examination [5]. The Rotterdam criteria state that patient must present with at least two out of three of (i) OD, (ii) HA, and (iii) PCOM to be diagnosed with PCOS. The stratification of patients using these three criteria resulted in the identification of four distinct phenotypes, namely A, B, C, and D, as illustrated in Figure 1. The Rotterdam criteria are the most widely accepted tool for the assessment of PCOS to date and have been updated with the International Evidenced-based Guideline on the Assessment and Management of PCOS 2018 and, more recently, in 2023, according to advances in scientific knowledge and technology [5,6]. However, the clinical phenotype has no influence on the standard-of-care therapeutics available to a patient who meets the Rotterdam

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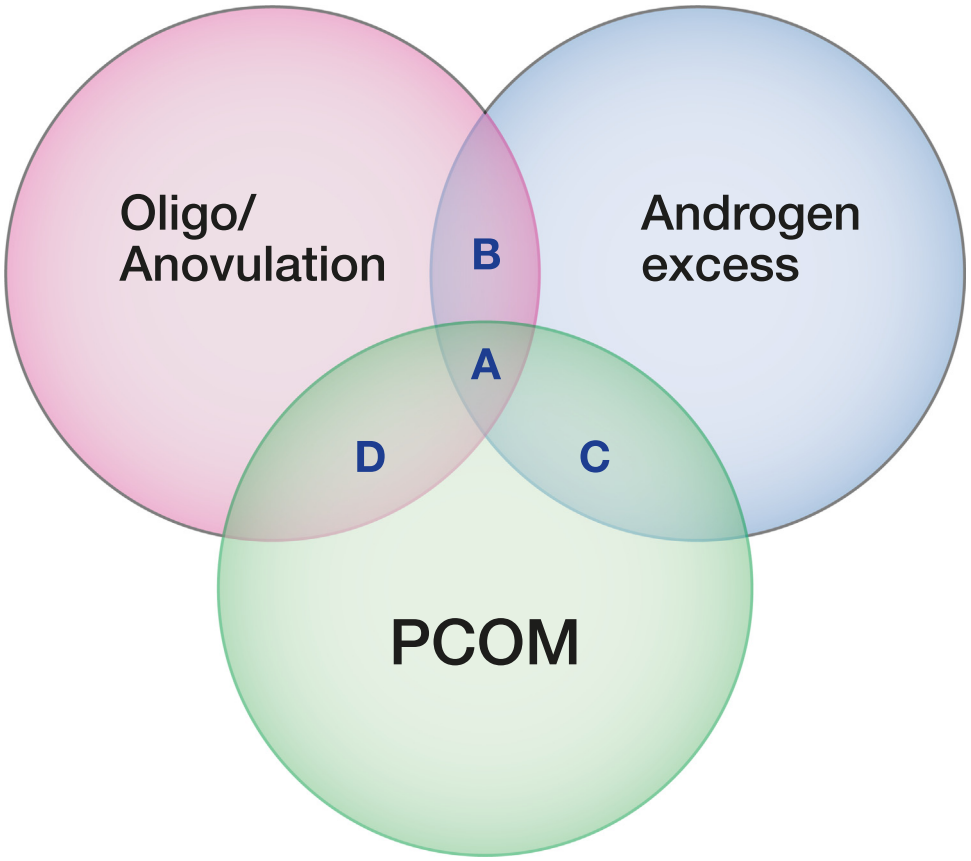

Figure 1. Classic Rotterdam criteria. A Venn diagram showing the relationship between the four Rotterdam phenotypes and the parameters used to diagnose polycystic ovary syndrome. Abbreviations: PCOM, polycystic ovarian morphology.

criteria for diagnosis of PCOS, with therapies treating the symptoms rather than the underlying etiopathology of each individual phenotype.

In 2006, the Androgen Excess-PCOS Society (AE-PCOS) expressed the opinion that the Rotterdam criteria were not entirely appropriate to yield a PCOS diagnosis, since it was thought that HA represented an integral characteristic of the syndrome. As such, AE-PCOS excluded Phenotype D as it was notably different from the other phenotypes and lacked signs of HA [7]. However, the AE-PCOS criteria have not been widely adopted [8].

The guidelines for identifying the three hallmarks of PCOS, as described by the Rotterdam criteria, are well defined but not without issues. As discussed later on in the text, numerous authors have criticized these criteria, with various updates having been made since their inception [9]. It is apparent that the Rotterdam guidelines have known issues with much room for interpretation, and it is the authors' opinion that these criteria may no longer be entirely appropriate for describing a diverse and complex syndrome. Furthermore, the identification of the four Rotterdam phenotypes has not led to specific treatments or personalized care. The international PCOS guidelines have been updated twice in recent years; however, it is of the authors' opinion that this falls short of highlighting the vital differences among the phenotypes. Therefore, as we approach the 20-year anniversary of the Rotterdam criteria, this Opinion lays the foundations for a possible reevaluation of the diagnosis and treatment of PCOS, asking if it is time for a rethink.

Glossary

Alopecia: the partial or complete baldness of hair where it would typically grow.
Androstenedione: a weak androgen involved in the production of estrogen and testosterone.
Anti-Müllerian hormone: a glycoprotein hormone, which is primarily involved in growth differentiation and folliculogenesis.
D-chiro-inositol (D-chiro-Ins): a stereoisomer of inositol, which is primarily involved in glycogen storage and the inhibition of aromatase-dependent conversion of androgens to estrogens. It is used in supplements as an insulin-sensitizer.
Dehydroepiandrosterone sulfate (DHEAS): an androgen involved in male puberty and the production of testosterone and estrogen in both men and women.
Follicle-stimulating hormone (FSH): a gonadotropin, which, in women, helps to the control of menstrual cycle and ovulation.
Hirsutism: the growth of terminal hair in a typical male pattern in women.
Homeostatic Model Assessment for Insulin Resistance (HOMA): a routine assessment used to evaluate insulin resistance and β-cell function, based on plasma insulin and glucose levels. A value greater than 2.5 typically denotes insulin resistance.
Hyperandrogenism (HA): the presence of elevated systemic or localized androgens beyond healthy levels. Typically, these androgens include testosterone, androstenedione, and DHEAS.
Insulin-like growth factor-1 (IGF-1): a growth hormone that is vital for human health. It is involved in cell growth, survival, and proliferation.
Insulin resistance (IR): a phenomenon where cells lose their normal sensitivity to insulin stimulation.
Liquid chromatography–mass spectroscopy: an analytical chemical technique used for the identification and quantification of chemical and biological samples on the basis of their molecular mass.
Luteinizing hormone (LH): a gonadotropin, which, in women, is involved in triggering steroid production in the ovaries and regulating the length of the menstrual cell cycle.
Myo-inositol (Myo-Ins): a stereoisomer of inositol, which is primarily involved with the transport of

Questioning the current phenotypical classification: the reliability of diagnostic tools

There is a common thought among researchers that, given differences in the phenotypes, the Rotterdam criteria should be revisited [9,10].

It has been claimed that flawed determination of androgen levels, faulty definitions of clinical symptoms, and more advanced imaging techniques have caused difficulties in prescribing the correct diagnosis and correctly characterizing patients according to the Rotterdam criteria.

The most common form of biochemical HA is elevated testosterone levels [11], primarily in a free form, unbound to **sex-hormone-binding globulin (SHBG)**, which is typically diminished in patients with PCOS because of factors such as obesity and **insulin resistance (IR)** [12,13]. Elevated testosterone levels are observed in the majority of patients (89% free testosterone, 49–80% total testosterone), in addition to increased levels of **androstenedione** and **dehydroepiandrosterone sulfate (DHEAS)** [14–17]. Measuring total or free testosterone is a common method used for identifying HA; however, these assays are known to be unreliable because of the low concentrations of testosterone typically seen in women, which vary throughout the day, in addition to steroid interference from similarly structured molecules such as DHEAS [18]. Thus it is advised that assays which use whole serum be avoided; instead, mass spectroscopy or immunoassays approaches should be taken, after extraction and purification by chromatography, which come with a higher degree of cost and complexity [6].

Clinical HA is characterized by **hirsutism**, acne, and androgenic **alopecia**. Hirsutism affects 60–70% of PCOS patients [19], and is the primary measure for diagnosing clinical HA, which is identified by a modified Ferriman–Gallwey score of ≥8 [20]. However, issues arise regarding the ethnicity of the patient and its correct implementation. The use of race-specific cutoff scores determined from an unselected population have somewhat alleviated these concerns, with a cutoff of 8 used when appropriate racial data are not available [21]. The use of hair removal products has brought the modified Ferriman–Gallwey scoring system's reliability into question, as it is reliant on the patients' self-reports which may not be entirely be accurate [22,23]. Acne and androgenic alopecia are also common clinical manifestations of HA; however, these suffer from a lack of specificity to facilitate a diagnosis of PCOS [24].

Oligo- or amenorrhea presents as the irregularity of the menstrual cycle [6], and the Rotterdam criteria currently diagnose oligomenorrhea as cycles >35 days apart or <8 cycles in a year. Often, if a suspected PCOS patient does not present with an altered menstrual cycle, the levels of serum progesterone and **luteinizing hormone (LH)** are assessed to identify the possibility of ovulatory dysfunction without oligo- or amenorrhea [25]. More inclusive definitions have been argued for, including patients with more frequent menstrual cycles, as this can be a sign of elevated testosterone and serum **anti-Müllerian hormone (AMH)** levels, which tend to occur in PCOS patients [26].

The Rotterdam criteria define PCOM as 12 follicles measuring 2–9 mm per ovary and an ovarian volume of >10 mL. It should be noted that as newer transvaginal ultrasound technology with a transducer frequency of 8 MHz has become available, 30–50% of healthy women would also be diagnosed with PCOM under this criterion [27]. In 2014, the AE-PCOS society redefined the criteria for PCOM, adjusting the threshold to ≥25 follicles per ovary and/or an ovarian volume of ≥10 cm^3. However, this was seen as an overcorrection; therefore, in 2018, the International Evidence Based Guidelines for the Assessment and Management of PCOS were changed once more to ≥20 follicles per ovary and/or an ovarian volume of ≥10 cm^3.

glucose into the cell and is involved in various signaling pathways involving hormones, neurotransmitters, and growth hormones. It has shown efficacy in treating PCOS.

Oligo- and amenorrhea: two types of abnormal menstruation. Oligomenorrhea refers to infrequent periods, while amenorrhea refers to the absence of periods.

Oral contraceptive pills (OCPs): a routine form of contraceptive, which typically prevents pregnancy by stopping ovulation and thickening the cervical mucus.

Ovulatory dysfunction (OD): unregular function of the ovary, typically observed through disruption of the menstrual cycle.

Polycystic ovarian morphology (PCOM): the presence of arrested follicles, typically referred to as 'cysts', identified through an ultrasound evaluation.

Polycystic ovary syndrome (PCOS): a common endocrinological–metabolic condition in women of reproductive age. Patients typically present some combination of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology.

Sex-hormone-binding globulin (SHBG): a glycoprotein involved in the transport of androgens and estrogens in the blood.

Challenging the definition and diagnosis of PCOS

As highlighted earlier in the text, in 2006, there was an attempt by the AE-PCOS to formally separate the classification of PCOS between those that fit the classic metabolic–endocrinological diagnoses (A, B, and C) and D, which does not fit into these criteria. Members of the PCOS community have taken issue with the name PCOS, as it gives too much attention to ovarian cysts, which are not always required for the diagnosis of the condition.

The rate of IR may correlate with the 'severity' of PCOS, with higher levels observed in Phenotypes A and B (80%), Phenotype C (65%), and Phenotype D (38%) [28], suggesting that dysregulation of the metabolism may play a role in HA being observed [29]. Furthermore, while IR can present in patients with Phenotype D, the lack of HA and the relatively lower levels of IR may suggest a different underlying etiopathogenesis. As such, Gleicher *et al.,* have argued for a simplification of PCOS, splitting the condition into HA+ and HA– PCOS [30]. It has also been suggested that it is not Phenotype D that should be excluded from the term PCOS, as it is the only phenotype that is likely to be a consequence of ovarian issues, but rather Phenotypes A, B, and C. Previously, we have put forward the term 'endocrine–metabolic syndrome', as this may more accurately represent the condition [31]. The new criteria are explained further in Figure 2.

The positive correlation between PCOS and IR has been long discussed and was observed clinically in 2019 [28,32]. Through the use of **liquid chromatography–mass spectroscopy** measurements, higher levels of total testosterone were seen in patients with IR. As a result of systemic IR, total insulin levels are elevated; however, in such cases, ovarian tissue retains its sensitivity to insulin, in what some have described as the 'ovarian paradox' [33]. *In vitro* experiments have shown that the consequent increased insulin levels continue to stimulate ovarian steroidogenesis in addition to LH-stimulated androgen secretion, thus leading to hyperandrogenism [34]. While

	PCO-EMS type 1 (Formally PCOS phenotype A)	PCO-EMS type 2 (Formally PCOS phenotype C)	EMS (Formally PCOS phenotype B)	PCOS (Formally PCOS phenotype D)
Hyperandrogenism Insulin resistance	✓	✓	✓	✗
PCOM Endometrial thickness	✓ <5 mm	✓ <5 mm	✗ <5 mm	✓ >5 mm
Menstrual cycle alteration	✓	✗	✓	✓
Dermatological symptoms	Acne, alopecia, hypertrichosis			✗
Related risk	Diabetes, hypertension, infertility			Infertility, endometrial hyperplasia, endometrial carcinoma

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Figure 2. Unfer classification of post-Rotterdam phenotypes, adapted from Unfer *et al.* [31]. The criteria for classifying hyperandrogenism, polycystic ovarian morphology (PCOM), and alterations of the menstrual cycle are consistent with the International Evidence-based Guideline on the Assessment and Management of PCOS 2023. The cutoff point for insulin resistance is calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA), with a value of over 2.5 considered insulin-resistant. Abbreviations: EMS, endocrine metabolic syndrome; PCO, polycystic ovary.

the causality between IR and HA in PCOS is still up for debate, a clear relationship of PCOS Phenotypes A, B, and C with IR hints at a possible etiopathogenesis for these phenotypes, whereby metabolic alterations seem to be heavily involved [35]. It therefore begs the question as to whether IR or hyperinsulinemia should be included in the criteria for PCOS, and the treatment adjusted accordingly. Moreover, if Phenotype D is not a metabolic endocrinological disorder, what is the underlying cause and how does this change the treatment choices for patients?

It has been theorized by the authors that in the absence of HA, the development of OD and PCOM in Phenotype D patients may be dependent on other biochemical abnormalities, such as growth factors [31]. **Insulin-like growth factor 1 (IGF-1)** and gonadotropins influence follicle growth and gynecological physiology (Figure 3) [36]; therefore, alterations in their levels may cause disruptions in follicles' maturation. Evidence of this possible explanation of PCOM in PCOS Phenotype D patients has been demonstrated in animal models, with excessive IGF-1 inhibiting proper follicle growth in mice; however, the precise mechanism behind this phenomenon is still unknown [37].

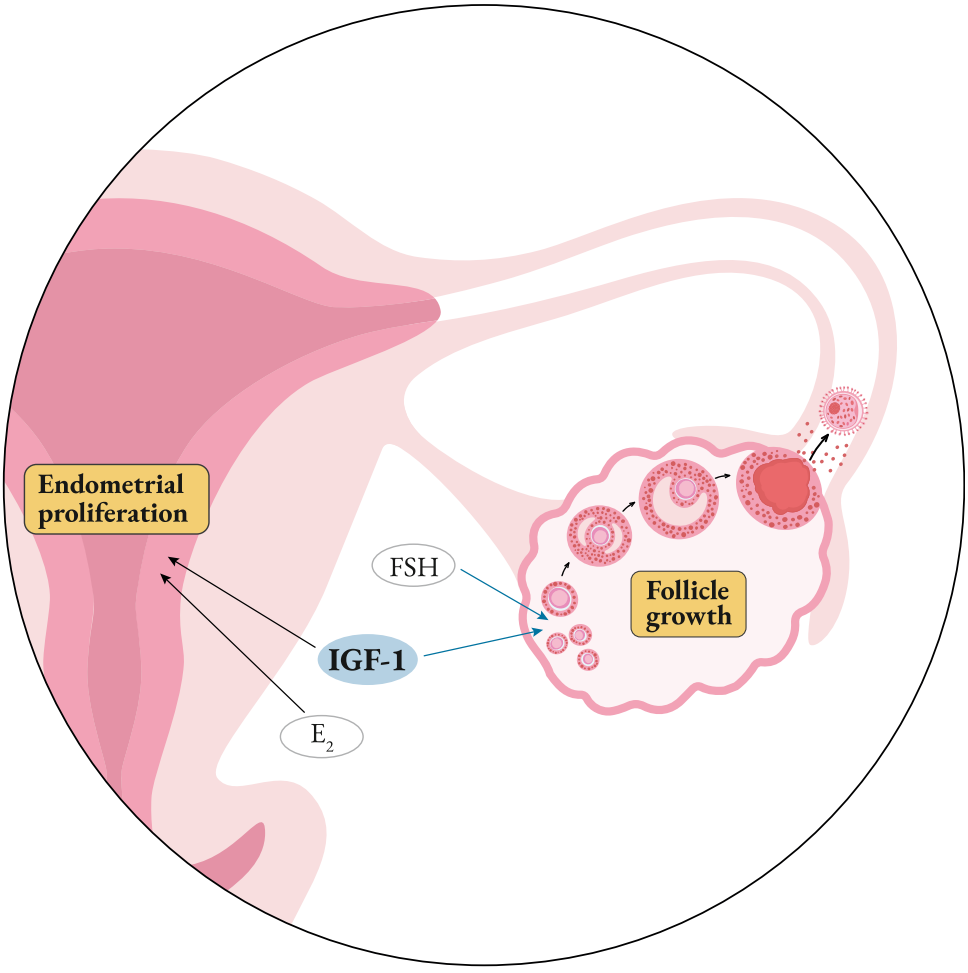

Figure 3. Physiological activities of Insulin-like growth factor 1 (IGF-1) in the female reproductive system. IGF-1 in the ovary stimulates follicle growth and encouraging proliferation enhanced by the presence of the follicle-stimulating hormone (FSH). IGF-1 promotes the proliferation of the endometrium, and its activity is favored by the stimulus of estrogens, particularly estradiol (E2).

Whilst there is no current evidence to associate alterations in IGF-1 levels with phenotype D PCOS, it provides a possible explanation for this normoandrogenic phenotype, meriting further investigation. Despite this plausible theory, the impairment of hypothalamic–pituitary communication cannot be excluded at this time.

Naturally, the reclassification or renaming of a pathological condition is not without difficulty or risk. It is of vital importance to include healthcare providers, advocacy groups, and researchers, as many of these have built careers and identities based upon specific naming conventions [38]. Furthermore, patients must be considered in such changes so as to not add confusion to a syndrome which has historically been poorly understood. However, we believe this change is necessary to solidify the difference between the HA phenotypes and the normoandrogenic Phenotype D, which appears to be dramatically different. Currently, Phenotype D is routinely considered to be 'less severe', with the phenotypes seemingly on a sliding scale [39]. It is the opinion of the authors that this is not the case, and that by keeping the phenotypes under the term 'PCOS', this may limit the therapies available for this patient subset. Moreover, the proposed name change may stimulate research into the etiopathogenesis behind these disorders, increasing knowledge in the field and leading to a higher level of personalized care.

What works for whom: tailoring treatment to phenotypes

To evaluate how the available treatment options vary among the phenotypes, we sought to interrogate the current standard-of-care therapies and evaluate their effectiveness.

Diet and exercise

The first suggested treatment for PCOS is a balanced diet, with obesity and IR frequently observed in PCOS. Elevated levels of saturated fats have been associated with an increased frequency of IR [40]. Obesity is known to be associated with Vitamin D deficiency, which directly and indirectly interferes with insulin signaling, worsening the effects of PCOS and its comorbidities [40–42]. This may be caused by the role Vitamin D plays in upregulating both the transcription and overall protein levels of insulin receptors, in addition to potentially causing an inflammatory response, potentially leading to IR [43]. In a meta-analysis of 11 studies conducted by Miao *et al*., Vitamin D supplementation in PCOS significantly reduced total testosterone levels and IR (**Homeostatic Model Assessment for Insulin Resistance (HOMA)**), in addition to total cholesterol levels [44]. Meanwhile, exercise helps to combat obesity and to reduce insulin and free androgen levels [45], leading to the restoration of a normal ovulation cycle through modulation of the hypothalamic–pituitary–gonadal axis.

Diet and exercise represent a lifestyle intervention, which has a beneficial effect on PCOS patients regardless of phenotype. However, this treatment improves the condition by ameliorating the metabolic profile of the patient; therefore, it may not have as profound an effect in patients who do not show dysmetabolism such as the majority of those presenting with Phenotype D.

Oral contraceptives

Oral contraceptive pills (OCPs) are a controversial first-line treatment for PCOS in women not seeking pregnancy [46]. OCPs treat the clinical manifestations of HA, improving OD, dysmenorrhea, and menorrhagia, and can be used to treat premenstrual syndrome and pelvic pain related to endometriosis and to prevent menstrual migraines [47]. Common side-effects of OCPs include mood changes and increased cardiovascular risk. In detail, the oral contraceptives levonorgestrel, desogestrel, gestodene, and drospirenone have been associated with a three- to sevenfold increase in venous thromboembolism; however, no pronounced cardiac risk was observed with progestin-only products [48]. Furthermore, the use of OCPs has been linked to worsening

of IR in obese patients [49]; therefore, alternative therapies such as weight loss and metformin have been suggested as preferable therapies. The primary mode of action of OCPs treats HA, so it should therefore be asked if this is the most appropriate treatment for Phenotype D.

Clomiphene, gonadotropins, and letrozole

Clomiphene is an ovulation-inducing agent, aimed at correcting the OD feature of PCOS. Resistance to clomiphene can occur and seems to be more common in HA+ PCOS phenotypes than in Phenotype D, suggesting it is more suited to this latter phenotype. However, given the low risk associated with the use of clomiphene, it is prescribed regardless of the PCOS phenotype. For patients who do not ovulate or conceive on clomiphene, gonadotropins such as **follicle-stimulating hormone (FSH)** represent a second-line fertility treatment for PCOS [50]. Letrozole is an aromatase inhibitor that has increasingly been considered as a first-line agent for inducing ovulation over clomiphene in recent years, with numerous meta-analyses comparing the efficacy of the two drugs [51]. A significantly higher rate of ovulation, paired with higher live birth and clinical birth rates, has been seen in letrozole versus clomiphene. Some concerns remain over the possible teratogenic effect on fetal development if administered during early pregnancy; however, these concerns are largely alleviated by letrozole's short half-life. To the best of our knowledge, no studies have investigated the differences in efficacy in gonadotropins or letrozole in the Rotterdam phenotypes.

Metformin

The use of insulin-sensitizing agents, such as metformin, has had success in PCOS for stimulating ovulation [52]. Metformin is routinely utilized in the treatment of Type 2 diabetes, and trials have demonstrated its efficacy in PCOS patients, causing a clear improvement in menstrual patterns, BMI, IR, androgen levels, ovulation, and pregnancy rates [53].

Metformin combats the IR-related symptoms of PCOS, treating the HA component of the condition [54]; however, the precise mechanism of its doing so is not entirely understood [53,55,56]. Therefore, the use of metformin in Phenotypes A, B, and C is clearly apparent; however, one would not expect metformin to have an effect in Phenotype D. To date, no clinical trials have compared the effectiveness of metformin across each phenotype.

Inositols

Inositol is a natural compound which exists as distinct stereoisomers, with **myo-inositol (myo-Ins)** and **D-chiro-inositol (D-chiro-Ins)** representing the two most commonly found in nature [57]. Both compounds are found in the ovaries and follicular fluid, playing a key role in mediating hormonal activities. The two isomers perform different tasks within the cell, and the maintenance of specific ratios between these is of utmost importance for cellular homeostasis, with disruption of this ratio disrupting the process of ovulation and leading to hyperandrogenism [58].

Inositols are primarily used as insulin sensitizers in the field of PCOS. Myo-Ins helps facilitate the activation of glucose transporters and glucose utilization, while D-chiro-Ins is involved in the synthesis of glycogen. Within the ovary specifically, myo-Ins regulates glucose uptake and FSH signaling, while D-chiro-Ins is responsible for regulating insulin-induced androgen synthesis [59]. As such, myo-Ins is routinely used in a variety of metabolic disorders including PCOS [60]. In fact, myo-Ins has demonstrated a similar efficacy to metformin, which is associated with known gastrointestinal side-effects; therefore, myo-Ins may offer an alternative approach [61]. Furthermore, in PCOS patients with IR, especially those who are overweight or obese, the use of a ratio of 40:1 of myo-Ins to D-chiro-Ins has also demonstrated success. In a study conducted by Nordio *et al*. investigating the effect of inositol treatment in overweight and obese women,

myo-Ins supplementation was compared with a 40:1 ratio of myo-ins/D-chiro-Ins [62]. In this study, over a 6-month treatment period, the myo-Ins/D-chiro-Ins group demonstrated a significantly quicker response to the therapy compared with MI alone, with a marked difference in metabolic parameters such as fasting insulin and HOMA after 3 months of treatment. Furthermore, the myo-Ins/D-chiro-Ins group showed a significant reduction in androgen levels, specifically total and free testosterone, and DHEAS, with an increase in SHBG. However, it should be noted that after 6 months of treatment, no significant difference could be observed between the two study groups.

The use of inositols is currently considered to be an experimental therapy (https://www.monash.edu/medicine/mchri/pcos/guideline); however, the use of myo-Ins is well validated in PCOS, as demonstrated by the studies reported in the preceding text. However, for Phenotype D, the question must be asked whether this treatment has merit, as inositol treatment addresses the HA associated with metabolic irregularities. It is therefore thought by the authors that this approach is unlikely to show efficacy in Phenotype D. Recently, the efficacy of myo-Ins was evaluated in HA and normoandrogenic PCOS, where it was observed that myo-Ins therapy was significantly more effective in terms of regulating glucose levels, HOMA, testosterone, SHBG levels, and the LH/FSH ratio in HA PCOS versus the normoandrogenic group [63]. A further finding from this work was that the endometrial thickness had a median value of 8 in the normoandrogenic cohort compared with 3 in HA PCOS patients at the beginning of the trial. No change was observed in the PCOS Phenotype D group, while after 6 months of treatment, endometrial thickness was restored in the HA group. Consequently, Unfer *et al*. included endometrial thickness in their proposed criteria outlined previously and within this article [31].

Outstanding questions

If PCOS Phenotype D is not a consequence of metabolic irregularities, what is the etiopathogenesis of this phenotype?

Can IGF-1 levels explain the ovarian OD seen in Phenotype D?

Should insulin status be considered when grouping patients into phenotypes?

With some conventional therapies perhaps showing limited efficacy in Phenotype D, what are the therapeutic options for these patients?

Should the Rotterdam criteria be merely updated, or should the community settle on a new set of criteria for treating and stratifying patients? If so, what should these criteria be?

How do gonadotrophin levels and AMH differ between the Rotterdam phenotypes, and how would this affect a revision of the criteria?

Concluding remarks

The current range of therapeutics is aimed towards the treatment of HA+ PCOS Phenotypes A, B and C; however, they do not adequately address the needs of PCOS Phenotype D patients (see Outstanding questions). This is especially true for therapies that treat PCOS from a metabolic angle, such as the use of metformin and inositols. New criteria for PCOS are required to properly divide patients, so that study groups more accurately reflect patient populations and correct therapies can be assigned. We hope this Opinion can aid discussions in the development of new criteria and spark interest in the development of novel therapies tailored towards Phenotype D for which there is a dire need.

Funding

No additional funding supported the writing of this article

Declarations of interest

S.H.M., M.R., S.D., G.F., and V.U. are employees of Lo.Li Pharma s.r.l

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