



# Delphi consensus on the diagnostic criteria of polycystic ovary syndrome

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## Abstract

**Purpose** To gather the current opinion among Italian gynecologists and endocrinologists regarding the definition, diagnosis, and treatment of polycystic ovary syndrome (PCOS).

**Method** A Delphi survey consisting of 26 statements was designed by a nine-member panel (consisting of members from the Italian Society of Endocrinology (SIE) and the Experts Group AQon Inositol in Basic and Clinical Research and on PCOS (EGOI-PCOS)) and distributed to 102 experts in PCOS across the fields of gynecology and endocrinology. Consensus was defined as an agreement between at least 70% of responders. Participants completed three rounds of statements, ranking their level of agreement.

**Results** Of the initial 26 statements, 25 reached an adequate consensus, with an overall response rate of 73%. The statements were divided into three sections: definition and current understanding, diagnosis, and treatment. Of the statements that reached consensus, near total agreement was reached in the first two sections, whereas there was a divergence of opinion in terms of optimum treatment strategy between the gynecology and endocrinology subgroups.

**Conclusion** It was agreed that the current clinical guidelines are inadequate for clinical and scientific practice, with most responders advocating for the inclusion of metabolic factors. Furthermore, the consensus opinion advocated for the diversification of hyperandrogenic vs. non-hyperandrogenic phenotypes. This survey gives a snapshot of the current understanding of PCOS in the Italian healthcare community.

**Keywords** Polycystic ovary syndrome · Hyperandrogenism · Insulin resistance · Delphi method

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## Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine condition observed in women of reproductive age, with a worldwide prevalence of between 10 and 13% [1]. Typically characterized by a combination of clinical and biochemical hyperandrogenism, menstrual cycle disruption, and the presence of arrested follicles (commonly referred to as “cysts”), patients with PCOS may suffer from a series of hormonal, metabolic, cardiovascular, and psychological comorbidities [2]. Since its description in 1935 by Stein and Leventhal [3], numerous international societies have sought to classify PCOS, in order to aid diagnosis and treatment. These efforts began in 1990 with the National Institute of Health (NIH) criteria and were subsequently built upon with the Rotterdam criteria (proposed by the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine) in 2003, which described PCOS as a condition featuring 2 out of 3 of the following symptoms: clinical and/or biochemical hyperandrogenism, oligo-/anovulation, and polycystic ovary morphology (PCOM) [4]. The Rotterdam criteria have been updated several times in recent years, most notably in 2018 and later in 2023 via the creation of the PCOS international guidelines [5, 6]. In the most recent guidelines, a group of 39 international societies laid out evidence-based recommendations for clinical practice, providing several notable updates to the Rotterdam criteria including new guidelines for the use of ultrasound in PCOS, the use of anti-Müllerian hormone (AMH) as a diagnostic marker, and guidelines for adolescent PCOS.

While these guidelines represent groundbreaking work, various members of the PCOS medical community have argued for the inclusion of metabolic factors such as insulin resistance or overweight/obesity in the diagnostic criteria, as these conditions are frequently observed in patients [7]. Furthermore, hyperinsulinemia has been associated with the presence of hyperandrogenism and is more frequently observed in hyperandrogenic PCOS patients versus non-hyperandrogenic PCOS patients [8]. This difference in the metabolic status between hyperandrogenic and non-hyperandrogenic patients, has caused some authors to argue that these two groups of patients present two different conditions deriving from separate etiopathogenesis [9].

With the aim of gauging the opinion of the clinical community, the Experts Group on Inositol in Basic and Clinical Research and on PCOS (EGOI-PCOS) and the Italian Society of Endocrinology (SIE), gathered an executive board of nine members who recruited 102 medical doctors across gynecology and endocrinology, and conducted a Delphi consensus, with the aim of providing further context to this historically misunderstood condition.

## Methods

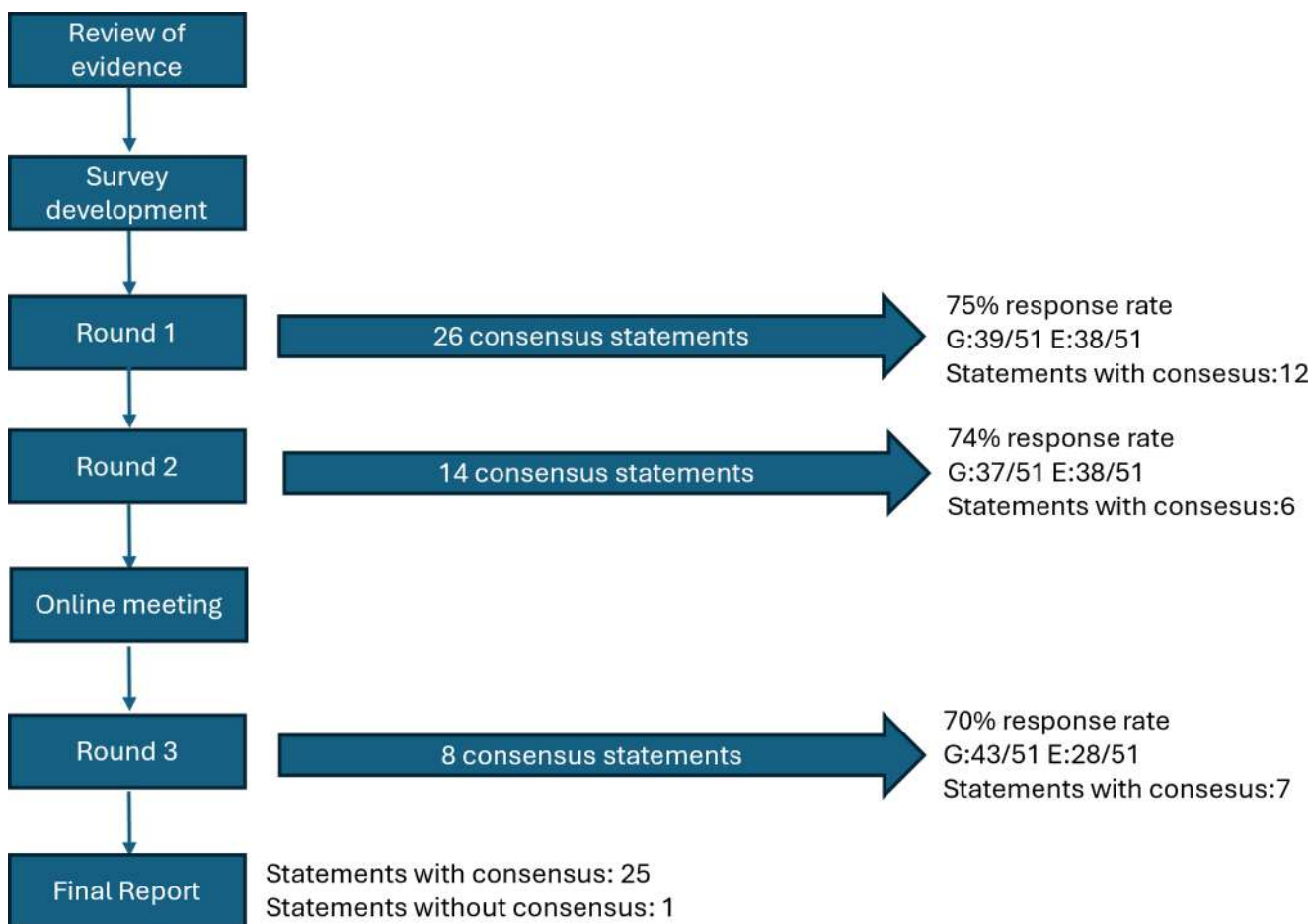
A group of 51 endocrinologists and 51 gynecologists, comprising of members of the EGOI-PCOS and SIE, were invited to take part in the Delphi consensus. Individuals were selected for their expertise in the clinical and scientific fields of gynecology and endocrinology. The survey process is outlined in Fig. 1, and adopted a modified version of the Delphi method [10]. In detail, an initial survey was put together by a non-voting nine-member executive board. This survey took into account existing literature and the clinical experience of the board members. 26 consensus statements were prepared, employing a voting system of 1–5 where 1 signified strongly disagree, 3 uncertainty, and 5 strongly agree (Likert scale). The survey was completed in Italian with the statements translated into English following completion of the work. These statements covered three larger subcategories: definition and current disease understanding, diagnosis, and treatment. Surveys were sent to the participants, completed, and the individual responses anonymized and pooled. Statements were said to have reached consensus when at least 70% of participants either agreed/strongly agreed or disagreed/strongly disagreed. The statements which had not reached consensus were reviewed and a report distributed among the participants. The remaining statements were then submitted to a second round; however, the voting system was restricted to three options: disagree, uncertain, or agree to assist the decision-making process. After the second round of statements total consensus was still not achieved; therefore, participants took part in a series of four online meetings and discussed the first two rounds. After this meeting, participants were asked to conduct a third round with the statements which had not reached consensus. Once this final round had been completed all statements which reached consensus, in addition to the one statement which did not reach consensus at the end of round 3, were incorporated into the final consensus report.

## Results

Response rates to the survey were as follows:

- 1st round: 39/51 gynecologist group and 38/51 endocrinologist group.
- 2nd round: 37/51 gynecologist group and 38/51 endocrinologist group.
- 3rd round: 43/51 gynecologist group and 28/51 endocrinologist group.

In total, 25 statements reached consensus whereas 1 did not; these responses are summarized in Figs. 2, 3 and 4.



**Fig. 1** Methodology flowchart describing the Delphi process employed in this work. G=Gynecology group, E=Endocrinology group

## Definition and current disease understanding

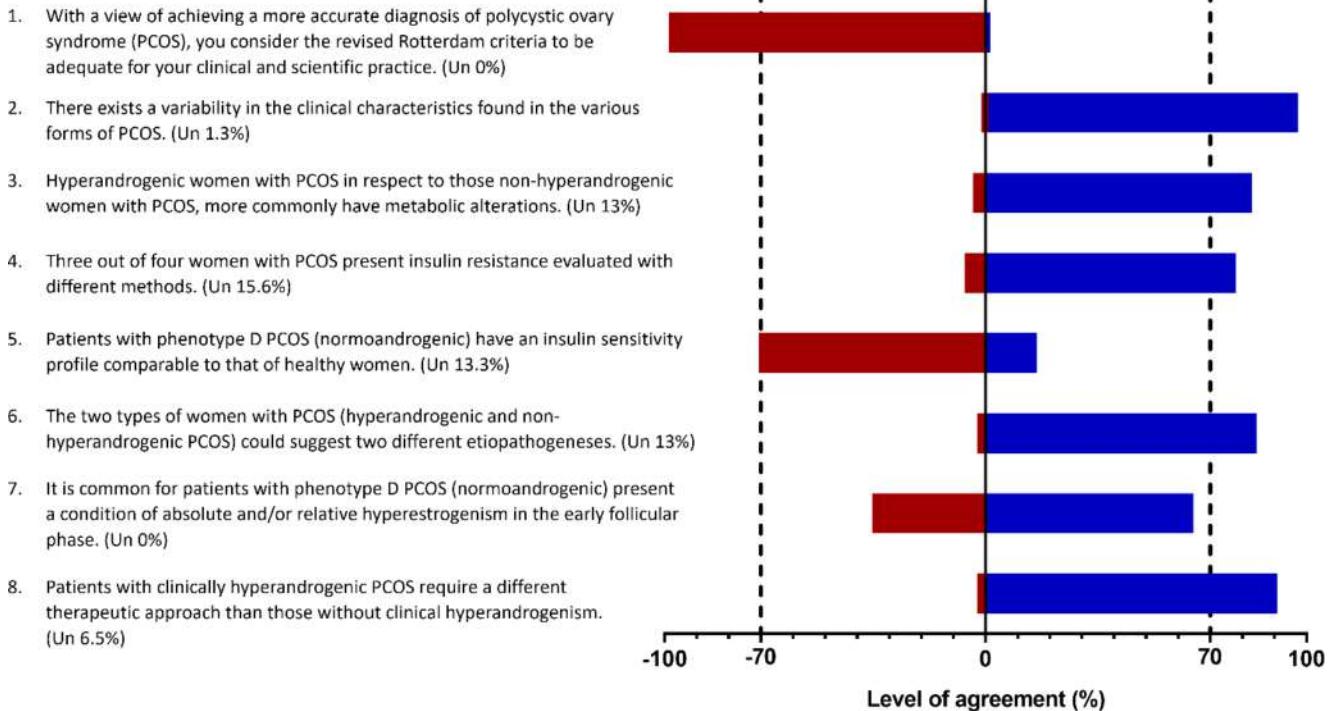
Among the professionals surveyed there was a 98.6% consensus that the Rotterdam criteria are not fully adequate for scientific and clinical practice, suggesting alternative improved criteria are required to improve patient care. There was a 70% agreement that three out of four women present insulin resistance, confirming it is a common comorbidity in patients with PCOS. A general agreement was reached that there exists a degree of clinical variability between forms of PCOS, in addition to the idea that hyperandrogenic women with PCOS are most commonly prone to metabolic alternations than women with non-hyperandrogenic PCOS. Considering these statements, it was also agreed that patients with hyperandrogenic PCOS may require a different therapeutic approach to those with non-hyperandrogenic PCOS, and that these two groups of patients may have a condition that derives from a different etiopathogenesis. However, it should be noted that the participants did not consider these non-hyperandrogenic patients to have a similar insulin profile to healthy women. In addition, no consensus could be

reached about whether non-hyperandrogenic PCOS patients demonstrate absolute or relative hyperestrogenism in the early follicular phase.

## Diagnosis

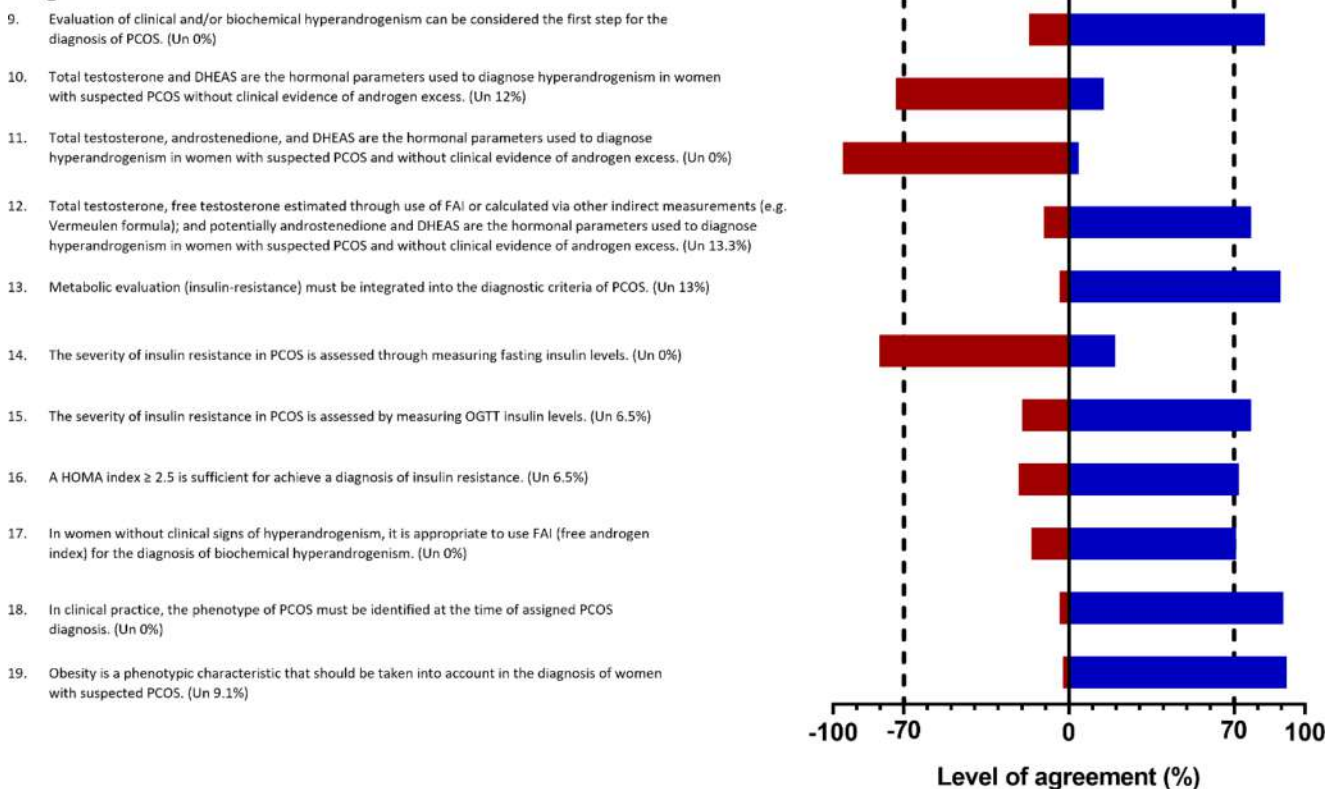
In terms of diagnosis, there was an 83.3% agreement in that evaluation of hyperandrogenism represents the first step in evaluating a patient for PCOS. There was consensus disagreement regarding evaluating hyperandrogenism via the measurement of total testosterone, dehydroepiandrosterone sulphate (DHEAS), and androstenedione, with most participants recommending that hyperandrogenism be evaluated using the free androgen index (FAI), with DHEAS and androstenedione having potential as diagnostic hormonal parameters. In total, there was a 92.2% agreement that metabolic evaluation in the form of measuring insulin resistance should be integrated into the current diagnostic criteria, with 72% of respondents agreeing that a homeostatic model assessment (HOMA)  $\geq 2.5$  is sufficient to define insulin resistance. However, most professionals surveyed

### Definition and current disease understanding



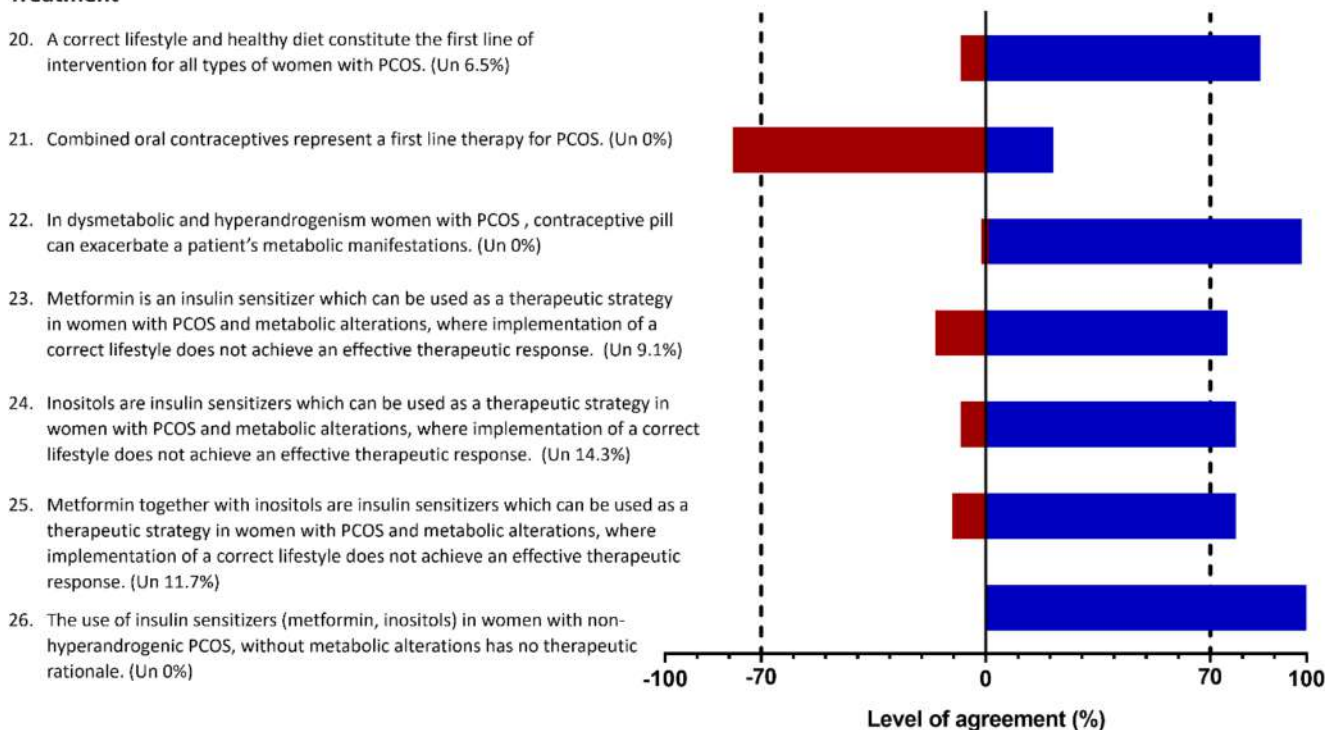
**Fig. 2** Comparison of the level of agreement and disagreement among questions regarding definition and current disease understanding of PCOS. Un=Uncertain

### Diagnosis



**Fig. 3** Comparison of the level of agreement and disagreement among questions regarding the diagnosis of PCOS. Un=Uncertain

## Treatment



**Fig. 4** Comparison of the level of agreement and disagreement among questions regarding the treatment of PCOS. Un=Uncertain

agreed that evaluation of insulin resistance should be preferably performed in the form of an oral glucose tolerance test (OGTT) instead of an evaluation of fasting insulin levels. Lastly, participants reached consensus that obesity should be considered in the diagnosis of PCOS, and that clinical phenotype should be assigned at the moment of diagnosis.

## Treatment

When asked about the best treatment options for women with PCOS, 85.7% of respondents agreed that lifestyle changes constitute the first line therapy in PCOS. There was consensus disagreement regarding the use of oral contraceptive pills (OCPs) as a first line therapy, and 98.1% of responders agreed that the use of OCPs may exacerbate the metabolic abnormalities routinely seen in PCOS patients. Consensus was reached on the use of insulins sensitizers, either metformin or inositols, for the treatment of metabolic abnormalities in PCOS where lifestyle changes are not sufficient. Notably, 100% of responders agreed that the use of either inositols or metformin did not have merit in patients with non-hyperandrogenic PCOS.

## Differences in consensus between gynecology and endocrinology groups

A sub-group analysis was performed to identify statements where sufficient consensus had been achieved, but within the individual gynecology or endocrinology subgroups the consensus did not reach 70%. In total 8 of the statements fell into this category (Fig. 5).

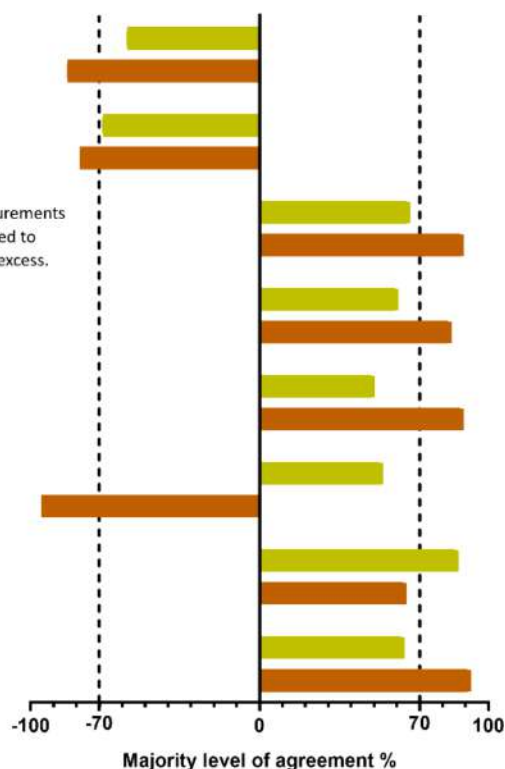
Notably, in these 8 statements:

- 6/8 statements: Leading majority from the gynecological group.
- 1/8 statements: Leading majority from the endocrinology group.
- 1/8 statements: Conflicting majority opinions.

To summarize this data, there was disagreement between the two groups as to the most appropriate androgen parameters to measure when evaluating biochemical hyperandrogenism as 78.4% of participants disagreed with the evaluation of only total testosterone and DHEAS in the gynecology group, while consensus was not reached in the endocrinology group. Similarly, 89.2% of gynecologists agreed with the use of total testosterone and FAI for the measurement of hyperandrogenism and androstenedione and DHEAS being potentially useful in the diagnosis, whilst once more no consensus was reached in the endocrinology group.

## Majority level of agreement comparison

5. Patients with phenotype D PCOS (normoandrogenic) have an insulin sensitivity profile comparable to that of healthy women. (Un 13.3%)
10. Total testosterone and DHEAS are the hormonal parameters used to diagnose hyperandrogenism in women with suspected PCOS without clinical evidence of androgen excess. (Un 12%)
12. Total testosterone, free testosterone estimated through use of FAI or calculated via other indirect measurements (e.g. Vermeulen formula); and potentially androstenedione and DHEAS are the hormonal parameters used to diagnose hyperandrogenism in women with suspected PCOS and without clinical evidence of androgen excess. (Un 13.3%)
16. A HOMA index  $\geq 2.5$  is sufficient for achieve a diagnosis of insulin resistance. (Un 6.5%)
17. In women without clinical signs of hyperandrogenism, it is appropriate to use FAI (free androgen index) for the diagnosis of biochemical hyperandrogenism. (Un 0%)
21. Combined oral contraceptives represent a first line therapy for PCOS. (Un 0%)
23. Metformin is an insulin sensitizer which can be used as a therapeutic strategy in women with PCOS and metabolic alterations, where implementation of a correct lifestyle does not achieve an effective therapeutic response. (Un 9.1%)
24. Inositols are insulin sensitizers which can be used as a therapeutic strategy in women with PCOS and metabolic alterations, where implementation of a correct lifestyle does not achieve an effective therapeutic response. (Un 14.3%)



**Fig. 5** A comparison of the majority consensus between the gynecology group (orange) and the endocrinology group (yellow), where one of the subgroups reached 70% consensus but the other did not

(65.8% consensus). Furthermore, 89.2% of gynecologists agreed with the use of only FAI for the evaluation of biochemical hyperandrogenism in women showing no clinical hyperandrogenism, while this number dropped to 50% in the endocrinologist group. In a similar manner there was disagreement in the suitability of the HOMA assay for the evaluation of insulin resistance with 83.8% of participants agreeing in the gynecology group versus 68.5% in the endocrinology group.

There was further disagreement regarding the typical insulinemic status of non-hyperandrogenic patients with PCOS, as in the gynecology group 83.3% of participants disagreed that these women had similar insulin levels to healthy controls, while there was less certainty in the endocrinology group (57.9% of participants disagreed with this statement).

Regarding optimum PCOS treatment, when asked about the status of OCP treatment as a first line therapy, 95.3% of the gynecology group disagreed with this statement; however, 53.6% of the endocrinology group agreed with this statement, demonstrating the largest delta in opinion between the two groups. In the context of insulin sensitizer use, the endocrinology group were more in favor of metformin use (86.8% agreement compared to 64.1% agreement in the gynecology group), whereas the gynecology group

advocated for the use of inositol treatment (92.3% vs. 63.2% agreement in the endocrinology group). Lastly, there was a higher overall level of consensus within the gynecology group (minority opinion: 7.5%; uncertainty: 4.9%; majority opinion: 87.9%) vs. the endocrinology group (minority opinion: 13.5%; uncertainty: 8%; majority opinion: 78.5%).

## Discussion

In the presented consensus, gynecologists and endocrinologists were surveyed with an average response rate of 73% between three rounds of statements.

One of the more notable observations was the consensus that the Rotterdam Criteria are not considered entirely suitable for scientific and clinical practice. In recent years these criteria have guided patient diagnoses, in addition to clinical trial recruitment and aided treatment choice. Despite a recent update, this survey suggests that this has not entirely translated into clinical care, at least considering a local level. In addition, there was an overall agreement in that there exists variability between the clinical phenotypes of PCOS and that hyperandrogenic PCOS patients demonstrate increased metabolic comorbidities. In a recent study conducted by Wen et al., the authors compared metabolic

abnormalities between patients with phenotypes B, C, and D, with the two hyperandrogenic phenotypes demonstrating a higher degree of metabolic irregularities compared to the non-hyperandrogenic phenotype [8]. In detail, the phenotype D group demonstrated a significantly decreased BMI, waist circumference, and waist-hip ratio. In contrast, hyperandrogenic PCOS was associated with elevated serum insulin concentration, HOMA index, total cholesterol, triglyceride, and low-density lipoprotein cholesterol, than the non-hyperandrogenic cohort. These trends have been observed in numerous other studies, with hyperandrogenism being associated with incidence of metabolic syndrome, increased HOMA, and worsened lipid profiles [11–13]. Similar conclusions were also reached in a study that measured insulin resistance by the gold standard hyperinsulinemic euglycemic technique and demonstrated that there is a scale of metabolic risk between the clinical phenotypes of PCOS [14]. Subsequent more detailed analysis showed that insulin-mediated substrate utilization is altered in women with PCOS, as compared to healthy controls, regardless of their phenotypes. However, this phenomenon was greater in subjects with A and B phenotypes, and in multivariable analysis free testosterone showed an independent role on insulin action abnormalities on both glucose and lipid metabolism [15]. It should be noted that although some authors have speculated the causality between metabolic alterations and PCOS, a definite causality has not been reported to date.

A consensus was reached regarding the statement that approximately three out of four women with PCOS present with insulin resistance, in agreement with figures quoted in literature which range from 65 to 95% [16]. In addition, considering that hyperandrogenic phenotypes are more likely to be insulin resistant than non-hyperandrogenic groups, this 25% of women with PCOS who do not present with insulin resistance may be reflective of the phenotype D cohort. This hypothesis is supported by the literature which states that the non-hyperandrogenic phenotype accounts for approximately 25% of the overall PCOS population; however, it should be noted that this number is dependent on geographic regions, with East Asian patients showing a higher prevalence of phenotype D [17, 18].

The involvement of metabolic factors in hyperandrogenic PCOS has led some in the scientific community to question whether hyperandrogenic and non-hyperandrogenic PCOS should be considered two separate conditions with separate etiopathogeneses. Accordingly, a positive consensus was reached within the surveyed group regarding this idea; however, it is notable that this opinion was much more prevalent in the gynecological group, as the endocrinological subgroup did not reach consensus. While the explanation for this divergence of opinion is not known, one potential explanation offered by the authors is that endocrinologists

typically encounter patients who fall into hyperandrogenic phenotypes (A, B, and C). Meanwhile, gynecologists typically encounter all phenotypes of PCOS, primarily due to issues regarding the menstrual cycle, thus this diverse patient pool may account for a different opinion regarding this statement.

In the presented work, one statement did not reach consensus, which was that phenotype D patients present a relative or absolute hyperestrogenism during the follicular phase. The rationale for the inclusion of this statement by the expert panel, stems from the increased androgenic and estrogenic state, which is observed in some patients with PCOS [19]. Furthermore, increased levels of estrogens are known to interfere with menstrual cycle regularity [20], and in the absence of biochemical hyperandrogenism, this could provide an explanation for the ovarian symptoms observed in this subset of patients. However, the lack of consensus demonstrates there is a lack of specific data from normoandrogenic PCOS patients to fully support this claim, demonstrating the need for further clinical studies. Despite this uncertainty, there was general consensus that phenotype D patients may require a separate therapeutic approach as compared to hyperandrogenic phenotypes. This idea is aligned with a general healthcare movement towards personalized medicine. It is for this reason that the EGOI-PCOS, a component of this Delphi consensus board, have recommended a formal renaming of the hyperandrogenic and normo-androgenic PCOS to endocrine-metabolic syndrome and multifollicular ovarian disorder [9, 21]. The rationale behind this proposed name change is to assist physicians in moving away from a “one size fits all” approach whereby phenotype D patients may be recommended medications, such as insulin sensitizers, which possibly have no therapeutic benefit.

The importance of hyperandrogenism for the diagnosis of PCOS was demonstrated by the high level of agreement, with the statement “*assessment of hyperandrogenism can be considered the first step of obtaining a diagnosis for PCOS*”. The inclusion of and/or in this statement suggests the importance of measuring both biochemical and clinical hyperandrogenism, which may not correlate. However, there was some level of disagreement on how this should be performed. While the collective survey group disagreed with the use of total testosterone, DHEAS, and androstenedione as the sole metrics to diagnose hyperandrogenism, and supported the use of FAI instead, a sufficient consensus was not reached within the endocrinology group. Furthermore, only 50% of surveyed endocrinologist agreed with the use of FAI to evaluate hyperandrogenism in patients not displaying clinical hyperandrogenism compared to 89.2% in the gynecology group. This data contrasts with the recently published international guidelines which supported

the use of FAI, further suggesting that these are not always being adhered to a local level. In support of this observation, a recent survey conducted among 500 European endocrinologists from the European Society of Endocrinology-ESE confirmed that the evaluation of hyperandrogenemia is not uniformly agreed upon and applied. According to the survey, most endocrinologists preferred to measure total testosterone (78.6%), followed by DHEAS (73.7%), FAI (56.4%), and androstenedione (55.8%), likely stemming from poorly defined threshold values and thus suggesting that the diagnostic relevance of each androgen needs to be established among endocrinologists in the field [22]. It is important to note that, while there are some concerns regarding the accuracy of testosterone assays routinely applied, they currently represent the most reliable and standardized tools to evaluate biochemical hyperandrogenism [23]. Regardless of the underlying explanation, the difference in opinion between gynecologists and endocrinologists among the surveyed professionals is indicative of how patient care can vary depending on the attending physician.

There was consensus that the evaluation of insulin resistance should be included in the diagnosis of PCOS. The most recent edition of the guidelines acknowledged the importance of metabolic comorbidities in PCOS but did not believe assays to detect insulin resistance were sufficiently reliable and are not recommended in routine care [6]. In this study, consensus was reached regarding the use of HOMA index to evaluate insulin resistance as a diagnostic criterion; however, it should be noted that upon subgroup analysis, the gynecology group had a higher degree of agreement (83.38% vs. 60.5% in the endocrinology group). This observation highlights a difference of opinion as to the reliability of HOMA index among medical professionals. This appears to be a controversial point, as although surrogate indexes of insulin resistance, based on either fasting or OGTT-derived glucose and insulin levels, are highly correlated with gold standard measures of insulin action, their ability in recognizing insulin resistant individuals is limited, particularly in terms of sensitivity, which may cause many subjects to be erroneously diagnosed as insulin sensitive [24].

A near on total agreement was reached that obesity should be considered a phenotypic characteristic of PCOS. Obesity and PCOS are closely associated with 38–88% of women with PCOS being overweight or obese [25]. To date obesity has not been included in diagnostic criteria for PCOS as, despite its prevalence, the condition can present in lean patients, although this is most prevalent in non-hyperandrogenic women with PCOS.

There was consensus agreement (90.9%) that the presented Rotterdam phenotype should be identified at the time of diagnosis. Not only would this allow individual patients to receive tailored care to their individual needs, but it would

also assist clinical research. Routinely, studies report that PCOS was diagnosed according to the Rotterdam Criteria or the 2018/2023 international guidelines for PCOS; however, individual phenotypes are not always described, hindering efforts to investigate their unique characteristics [26].

In terms of the treatment of PCOS, a majority of responders agreed that “*A correct lifestyle and healthy diet constitute the first line of intervention for all types of women with PCOS*” in line with the international PCOS 2023 guidelines. However, it should be noted that adherence to these recommended lifestyle changes is typically poor [27]. Moreover, up to 43% of women report that they are dissatisfied or indifferent with the information given about lifestyle management [28].

The largest divergence in opinion between gynecologists and endocrinologists regarded the use of OCPs as a first line therapy. OCPs have long been employed in the treatment of PCOS, as they can reduce androgen levels and regulate menstrual cyclicality. The use of OCPs is currently recommended by international clinical PCOS guidelines although it was noted that “PCOS specific features, such as higher weight and cardiovascular risk factors, need to be considered [6].”. The difference between the two subgroups in this consensus may be explained by gynecologists’ concern regarding long term usage of OCPs, as gynecologists are more likely to observe a patient at multiple stages of life (i.e., adolescence, adulthood, pregnancy, and menopause), while this is not as common in the field of endocrinology.

There was general agreement regarding the insulin sensitizers metformin and inositol in patients with metabolic alterations where lifestyle changes were not sufficient. It is interesting to note that metformin appears to be treatment of choice of endocrinologists, while inositol is preferred by gynecologists. A pair of studies, a meta-analysis and a systematic review, demonstrated no significant difference in the two treatments across BMI, fasting insulin, fasting blood sugar, HOMA index, and LH/FSH; however, myo-inositol demonstrated a better safety profile with minimal adverse effects compared to metformin, which is typically associated with gastrointestinal side effects [29, 30]. It is difficult to rationalize as to why there was a divergence in opinion between the two groups. One explanation may be found in the 2023 edition of the international PCOS guidelines, which highlighted myo-inositol as having potential in PCOS, but still classified the supplement as an experimental treatment falling short of formally recommending myo-inositol therapy, due to a limitation of available information and the urgent need for more evidence-based data [31]. Another potential explanation for this difference in opinion, is that Italian gynecologists have less experience prescribing metformin in comparison to endocrinologists, who are much more familiar with the drug.



Within this Delphi consensus there was a higher degree of variability in the responses to the statements amongst the endocrinology group. This may be reflective of the type of patients regularly encountered by the two types of specialists, or a higher degree of communication among gynecologists within the EGOI-PCOS, resulting in a common approach to the management of PCOS. It is plausible that the high degree of variability in the responses among endocrinologists is due to the high degree of ambiguity which still exists around the diagnosis and management of PCOS. It is therefore vital that well-designed and sufficiently powered studies are carried out appropriately address areas of ambiguity, and unmet needs within certain patient populations.

As with all works of this nature, this study has several limitations that are worth highlighting. The anonymous nature of the technique limits the opportunities for open discussion, whereby deeply entrenched opinions may not have space to be profoundly interrogated. Furthermore, this technique puts a heavy burden on the expertise of individual responders. Another limitation of this study is that the final round of consensus was overrepresented by gynecologists, which may introduce a degree of bias in the responses to the statements addressed in round 3. Moreover, as the questions were not changed between rounds of consensus, it is possible that a collective bias may be present in the later rounds. A further limitation of this work is that it did not address the use of ultrasound as a diagnostic tool for PCOS. This is noteworthy, given recent modifications to follicular number and ovarian volume cutoffs, in addition to the possible evaluation of AMH instead of the use of ultrasound for identifying PCOS in adults. Lastly, the presented work does not fully address all therapeutics options for patients with PCOS. Certain treatment options, such as anti-androgen therapy and cosmetic treatments (epilation, laser hair removal), were not discussed, presenting a limitation of this work.

## Conclusion

This Delphi consensus gives a snapshot of PCOS practice at the local level within Italy. It is apparent that the current clinical guidelines are not thought to be entirely suited to the patients' needs, with responders advocating for the inclusion of obesity and metabolic factors within the current diagnostic criteria. Interesting points of controversy within the surveyed group included the use of OCPs, and the etio-pathogenesis of non-hyperandrogenic PCOS, suggesting further research is required.

## Declarations

**Competing Interests** V.U is an employee of Lo.Li Pharma s.r.l, all other authors have no competing interests to declare.

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