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METHODOLOGY

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Diagnosis and management of infertility in patients with polycystic ovary syndrome (PCOS): guidelines from the Italian Society of Human Reproduction (SIRU) and the Italian Centers for the Study and Conservation of Eggs and Sperm (CECOS Italy)

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Abstract

The polycystic ovary syndrome (PCOS) is a multifaced disease of the reproductive age associated with several comorbidities including infertility. Very few documents regarding the management of the infertility in women with PCOS, including guidelines, position papers and consensus conferences, are available in the literature. The Italian Law indicates that health professionals must comply with the recommendations set out in the guidelines developed by public and private bodies and institutions, as well as scientific societies and technical-scientific associations of the health professions, except for specific cases. Unfortunately, no guideline for the diagnosis and the management of infertility in women with PCOS is currently available in Italy. In 2024, the Italian Society of Human Reproduction (SIRU) and the Italian Centers for the Study and Conservation of Eggs and Sperm (CECOS Italy) pointed out the need to produce Italian guidelines on this topic and established a specific working group to develop those guidelines. The working group chose to adapt the guideline with highest quality to the Italian context rather than developing a de novo document. The International Evidence-Based Guideline for the Assessment and Management of PCOS guidelines were selected. All recommendations regarding the diagnosis and the management of women with PCOS and infertility extracted, adapted to the Italian context and improved incorporating new recommendations or practical comments and suggestions where needed.

Keywords Guidelines, Infertility, Management, Polycystic ovary syndrome, PCOS

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Introduction

Polycystic ovary syndrome (PCOS) is a multifaced disease of the reproductive age associated with several comorbidities, including infertility [1]. Patients with PCOS frequently undergo diagnostic and therapeutic procedures for reproductive problems [2]. Ovulatory dysfunction, one of the criteria for PCOS diagnosis [3], is frequently associated with menstrual irregularities, especially oligo-amenorrhea, and is considered the main cause of infertility in women with PCOS [4]. However, several experimental and clinical findings underline that the fertility in women with PCOS may be also affected for abnormalities in endometrial [5] and oocyte [6] competence, irrespectively from ovulatory dysfunction.

Recent data seem to confirm that a correct therapeutic flow-chart, as suggested by available recommendations, can optimize the reproductive chances in women with PCOS allowing to reach a long-term fecundability like or slightly higher in comparison with women without the disease [7, 8].

In Italy, the Law n. 24 2017, indicates that health professionals must comply, except for specific cases, with the recommendations set out in the guidelines developed by public and private bodies and institutions as well as scientific societies and technical-scientific associations of the health professions. These guidelines must be developed following a scientific methodology [9] and approved by the National Center for the Clinical Excellence, Quality and Safety of the Care (CNEC, *Centro Nazionale per l'Eccellenza Clinica, la Qualità e la Sicurezza delle Cure*), an institutional organism directly referring to the Ministry of Health.

No specific guideline for the diagnosis and management of infertility in PCOS is currently available in Italy [10]. In 2015, an endocrinological and gynecological consensus statement of the Italian Society of Endocrinology was published [11]. That consensus statement reported in a narrative fashion few generic recommendations about the treatment of infertility in women with PCOS. In addition, the two main therapeutical innovations in the treatment of infertile women with PCOS, i.e. letrozole administration as ovulation inductor and GnRH antagonist use in in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI), were not contemplated [12].

Based on these considerations, the Italian Society of Human Reproduction (SIRU, *Società Italiana di Riproduzione Umana*) and the Italian Centers for the Study and Conservation of Eggs and Sperm (CECOS Italy, *Centri Conservazione Ovociti e Spermatozoi - Italia*) decided to produce an official document for the diagnosis and management of infertility in women with PCOS to be adopted in Italy. This report aims to detail the methodological process followed and the results obtained.

Methods

The methodology used agreed with the provisions of the National System Guidelines System (SNLG, *Sistema Nazionale Linee-Guida*) and all the steps were carried out in accordance with the specific Manual of CNEC (https://www.iss.it/documents/20126/7949265/Manuale+Metodologico+-+marzo+2023.pdf/01f4bc8e-f3e6-66ec-bbe1-e80186908c6c?t=1679921943422).

The initial idea to develop the guidelines was spread and shared among the members of the Society during the VII National Congress of the SIRU (Bari, 11th-13th April 2024) and was approved. A formal proposal for sharing and participation was made to CECOS Italy that approved the collaboration. In consideration of the experience previously acquired [10], no specific funding was defined and the SIRU and the CECOS Italy themself participated to cover the expenditures.

SIRU and CECOS Italy steering committees defined an integrated Working Group on Italian Guideline for Infertility in PCOS. That working group was defined according to principles of professional and specialist representation and excluding components that declared any potential important conflict of interest. It included citizens' and patients' associations, different professions (including lawyer, biologist, doctor, and midwife), and medical specialties (including medical genetics, obstetrics and gynecology).

The complete methodological process of elaboration of the guideline followed the "GRADE-ADOLOPMENT approach" based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) frameworks [13]. It was performed through meetings conducted in teleconferences for reducing the expenses/costs. Any disagreements were resolved by consensus methods.

According to the methodology already followed and previous experience [10], the Working Group chose to adapt, rather than to develop, available guideline of high methodological quality to the Italian context. Thus, the Working Group systematically searched recent available guidelines on the diagnosis and management of infertility in women with PCOS, assessed their quality, and selected the guidelines with the highest quality to use as reference. The search was conducted using key terms such as "polycystic ovary syndrome" or "PCOS" matched with "guideline", "consensus conference", "position paper", "position statement", "scientific statement" or "recommendation" on main websites, including PubMed, Web of Science, Google Scholar, Cochrane Library. All articles that referred to guidelines for the diagnosis and management of infertility in women with PCOS were screened without language restriction reading the full text. The

guidelines intercepted were then rated for quality using the Italian version [14] of the Appraisal of Guidelines for Research and Evaluation II (AGREE II) scoring system [15, 16], and the item with the highest AGREE II score was chosen as the reference document. That reference document was adapted (https://www.gimbe.org/pagine/569/it/agree-ii) deleting or changing recommendations considered not relevant, repetitive, debatable, or not/poorly applicable to the Italian context, and reporting the specific reason for each change (deletion or change). No specific attempt was planned and made to update the reference document.

The revised document was analyzed to identify new issues not assessed in the reference guideline, not previously addressed in the SIRU-guidelines for the diagnosis and management of infertility in Italy [10], and potentially relevant for the Italian context and from a clinical point of view. New clinical issues were defined using specific clinical questions and developed according to the Population, Intervention, Comparison and Outcomes (PICO) model [17]. Specifically, the "Population" comprised of infertile patients with PCOS, the "Intervention" encompassed each strategy, procedure, or treatment employed to diagnose or treat infertility in women with PCOS, the "Comparison" involved neither intervention (diagnostic and/or therapeutic) nor a placebo/sham arm or another potentially active intervention, and the "Outcomes" were ranked by importance in evaluating intervention effects case-by-case using three main categories, i.e. critical, important but not critical, and of limited importance.

Using the same websites mentioned above, a further extensive search of published studies was performed for each item using the hierarchy of evidence starting from systematic reviews and meta-analyses, randomized controlled trials (RCTs) up to experimental data or expert opinion, and the highest evidence was used. Each study was analyzed, and the certainty of evidence and the study quality was defined using specific tools. Data published up to August 19, 2024, were collected, analyzed, interpreted, and integrated into the referral guideline.

Each new item of the document was reported according to the GRADE system (https://gdt.gradepro.org/app/handbook/handbook.html) to rate the quality of evidence and the strength of recommendations using a direct and standardized language and graphical descriptions to improve simplicity and transparency. The methodology used was optimized after the selection of the available guideline to harmonize the document (Table 1).

The text including specific recommendations for infertile patients with PCOS was summarized integrating the different items in operative and integrated document for its largest diffusion and applicability.

The document was subsequently subjected to a public consultation with the aim of collecting feedback on the preliminary version of the recommendations, as well as to evaluate their applicability and feasibility. Specifically, the document was announced by email to SIRU and CECOS Italy members and potential stakeholders. Then, it was published for two weeks on the SIRU's website (https://www.pmaumanizzata.com) to receive further comments and additional suggestions. The participants to public consultation included bioethicists, biologists, endocrinologists, gynecologists, oncologists, immunologists, midwives, psychologists, citizens and patient representatives, and pharmaceutical and biomedical industry representatives. It was asked to provide personal, professional, and contact data, and to list any changes suggested to the clinical recommendations, indicating the related reasons, including possible obstacles to their application, and any useful reference. The Working Group analyzed the suggested changes and integrated those deemed appropriate in the final document.

After the public consultation, the document was submitted to an external review to improve the quality of the document and to collect feedback on the draft version of the recommendations. Two well-recognized international experts were identified, contacted and asked to revise the final document. The Working Group assessed the suggestions and comments received and included those considered relevant in the final version of the document.

The SIRU decided to update the guidelines every two years to integrate new scientific evidence to support modifying pre-existing recommendations or to draft novel recommendations, and to submit the final document to Reproductive Biology and Endocrinology for the normal process of international peer reviewing.

Results

The Fig. 1 details the entire methodological process followed to produce an official document for the diagnosis and management of infertility in women with PCOS in Italy.

After online search and evaluation of the available guidelines, the Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of PCOS [3] resulted to have the highest AGREE II score and were selected as the guiding reference for this project. The full details on the methodological aspects, the technical evidence and administrative reports of those recommendations are available online on the following website: www.monash.edu/medicine/mchri/pcos.

These recommendations [3] are international guidelines involving all aspects of the PCOS, organized in sections, and covering five specific areas of interest,

Table 1 The grading of the quality of evidence and the strength of recommendations are here reported together with the graphical descriptions and the terminology used. This methodology was the same used in the referral guideline [3] to harmonize the final document with the regard of the new clinical items analyzed

Certainty of evidence		
Graphical descriptions	**Grading**	**Meaning**
⊕◯◯◯	Very low-quality evidence	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect
⊕⊕◯◯	Low quality evidence	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect
⊕⊕⊕◯	Moderate quality evidence	Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕⊕⊕	High quality evidence	Very confidence in the effect estimate: the true effect lies close to that of the estimate of the effect
Strength of recommendation		
Graphical descriptions	**Grading**	**Terminology**
♦	Conditional recommendation against the option, there is lack of appropriate evidence or harms may outweigh benefits	"should not"
♦♦	Conditional recommendation for either the option or the comparison, the quality was limited, and the benefits of the option did not exceed clearly the harms	"could consider"
♦♦♦	Conditional recommendation for the option, the quality was limited, and available studies demonstrate little clear advantage of the option in terms of benefits / harms ratio	"should consider"
♦♦♦♦	Strong recommendation for the option, the benefits of the option exceed the harms	"should"
Terminology to categorize the recommendations	**Meaning**	
EBR: evidence-based recommendation	The evidence was sufficient to inform a recommendation made, good clinical practice (high quality evidence for every day clinical activity)	
CR: consensus recommendation	The evidence was not sufficient to inform a recommendation made (or only data from the general population are available), "expert opinion" (option not supported by direct evidence, but potentially useful for the clinical practice)	
PP: practice point	The evidence from the PCOS and/or general population was not available about important clinical topics and the consensus recommendation was arbitrarily made, "expert opinion" (option not supported by direct evidence, but potentially useful for the clinical practice)	

The strength of recommendation is the result of the overall interpretation and practical application of the recommendation, balancing benefits and harms (quality, feasibility, acceptability, cost, and implementation). The definition for the two "conditional recommendations" was better distinguish from original paper by Teede et al. [3]

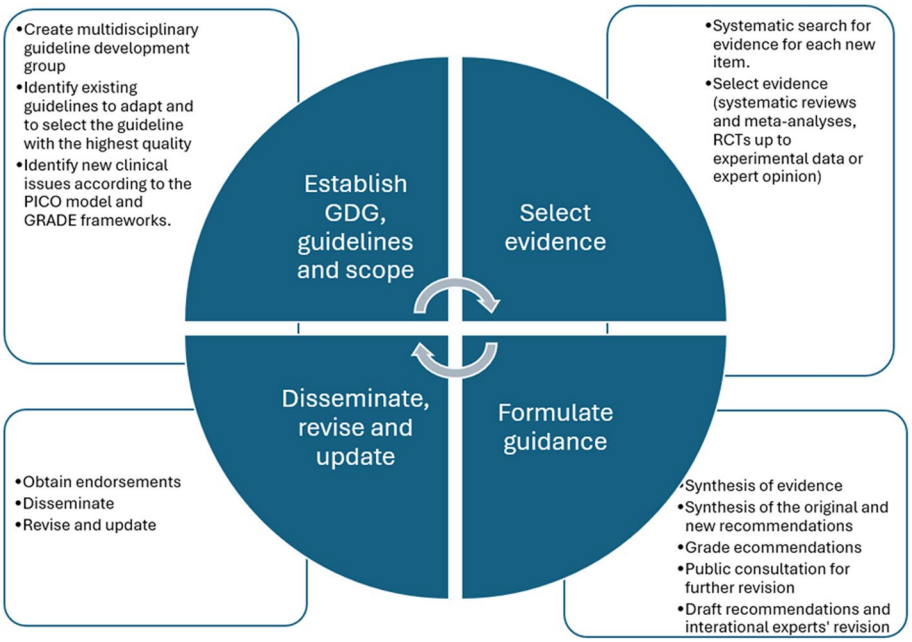

Fig. 1 Guideline development process. PICO model: Population, Intervention, Comparison and Outcomes model; GDG: Guideline Development Group; GRADE frameworks: Grading of Recommendations Assessment, Development and Evaluation Evidence to Decision frameworks; RCTs: randomized controlled trials

including screening, diagnostic and risk assessment and life stage; psychological features and models of care; lifestyle management; management of nonfertility features; and assessment and management of infertility.

Initially, the Working Group extrapolated section number five titled "Assessment and management of infertility". This section was used as the initial document. Other recommendations originally reported in the other sections [3] were selected if considered relevant for making more complete the new document. The total items initially included in the analysis were 116. Specifically, 60 and 56 items for Sect. 5 and for all other sections, respectively, were extracted.

All original recommendations extracted were analyzed for relevance and applicability to the Italian context, contextualized to adult infertile women and accordingly modified. Redundant/repetitive items were also deleted. After the revision process, a total of 93 items remains in the document (Supplementary Table 1). These items resulted modified from the original version in 24 (40%, 24/60) and 34 (61%, 34/56) cases for Sect. 5 and for all other sections, respectively. The quality of evidence and the strength of recommendations did not change for the revised/adapted items in comparison with the original one.

Secondly, the Working Group identifies new issues not assessed in the reference guideline [3] and considered potentially relevant from a clinical point of view. Table 2 reports these new critical topics as questions and their answers. As already mentioned in the Methods section, a similar methodology used in the original paper [3] and following to the GRADE system (https://gdt.gradepro.org/app/handbook/handbook.html) was applied for these new areas of clinical interest to harmonize the document with special regard for the terminology, the quality of evidence and the strength of recommendations (Table 1).

The public consultation of the SIRU-CECOS Italy guideline was attended by external reviewers, including biologists, medical doctors (endocrinologists and gynecologists), midwives, psychologists, representatives of citizens, patients, and pharmaceutical and biomedical industries. During this phase, the items previously defined have been subject to minor revisions; however, their total number and content were unchanged.

After revisions following the public consultation, the document underwent further revision by two international experts. Specifically, dr. Raoul Orvieto (Sheba Institute of Tel Aviv, Israel) and dr. Didier Dewailly (University of Lille, France) were invited to revise the recommendations/suggestions adapted from reference document (Supplementary Table 1) and the new recommendations/suggestions (Table 2). The Working Group prepared a comprehensive response to the Reviewers' comments. The Reviewers' suggestions were included when considered relevant. Specifically, a total of 38 suggested revisions were addressed, of which 24 were accepted and 14 rejected. After international experts' revisions, 5 and 3 items were modified and deleted, respectively, from the adapted items of the referral document [3], while 3

Table 2 New issues not specifically assessed in the reference guideline [3] and considered potentially relevant from a clinical point of view. These new topics are presented as clinical questions

1.How to diagnose PCOS?
1a.EBR – The diagnosis of PCOS should be based on the presence of at least two of the following three criteria: (a) clinical and/or biochemical hyperandrogenism, (b) polycystic ovarian morphology, and (c) irregular menstrual cycles, after exclusion of other causes of hyperandrogenism and/or irregular menses. ❖❖❖⊕⊕⊕◯

2.Is hysteroscopic assessment needed in infertile patients with PCOS?
2a.CR – Hysteroscopic assessment should not be considered as routinary evaluation for diagnostic work-up in infertile patients with PCOS. ❖
2b.CR - Hysteroscopic assessment should be considered in infertile women with PCOS according to clinical data and ultrasonographic findings in consideration of the higher risk of endometrial premalignant/malignant diseases. ❖❖❖

3.Which are the protocols for administering CC, letrozole, and metformin?
3a.CR - CC should be administrated using an escalation regimen, starting from lowest up to highest doses (from 50 mg to 150 mg daily) for five days, starting in the early proliferative phase (2^{nd} - 3^{rd} day of the menstrual cycle). ❖❖❖
3b.CR - Letrozole should be administered in an escalation regimen, starting from lowest to the highest doses (from 2.5 mg to 7.5 mg daily) for five days, starting in the early proliferative phase (2^{nd} - 3^{rd} day of the menstrual cycle). ❖❖❖
3c.CR – Metformin is available as immediate- and extended-release formulation:
- immediate-release metformin could be taken at meals, beginning with 500 mg at dinner for 3–4 days, and then increasing by 500 mg every 3–4 days up to a maximal dosage of 2000 mg daily ❖❖
- extended-release metformin (1000 mg) could be taken with the evening meal and a second dose could be added after one week with breakfast up to a maximal dosage of 2000 mg daily. ❖❖

4.How to define CC and letrozole resistance?
4a.PP – CC resistance should be diagnosed when 150 mg daily of CC for 5 days is ineffective to induce ovulation.
4b.PP – Letrozole resistance should be diagnosed when 7.5 mg daily of letrozole for 5 days is ineffective to induce ovulation.

5.How to define CC and letrozole failure?
5a.EBR - CC failure should be diagnosed in case of reproductive failure after 6 ovulatory cycles. ❖❖❖⊕⊕◯◯
5b.PP – Letrozole failure should be diagnosed when reproductive failure occurs after 6 ovulatory cycles.

6.Should oral ovulation induction treatments be started after progesterone withdrawal bleeding?
6a.EBR – After pregnancy exclusion, oral ovulation inductors could be administered without progesterone-induced uterine bleeding. ❖❖⊕◯◯◯

7.Should oral ovulation induction treatments be monitored in women with PCOS?
7a.PP - Ovulation induction treatments with CC with or without metformin should be monitored to minimize the risk of multiple pregnancy.
7b.CR – Ovulation induction with gonadotropin for non-IVF cycles should be strictly monitored to cancel cycles with a multiple follicular growth (more than two follicles) and minimize the risk of multiple pregnancy. ❖❖❖

8.How many ovulatory cycles should be performed before moving on to the next therapeutic step?
8a.PP – Before considering an IUI or IVF program, a total of 6-12 ovulatory cycles should be completed according to clinical context, risks, benefits, costs, timing and patient's individual preferences. Consider a period of 6 ovulatory cycles for women older than 35 years.

9.How to treat the infertile PCOS patient after failure of the ovulation induction?
9a.PP – Women with PCOS who did not achieve a pregnancy after 12 ovulatory cycles should be considered as patients with unexplained infertility, considering treatment options in relation to clinical context, risks, benefits, costs, timing and patient's individual preferences.

10.Is it necessary to perform male and tubal factor assessments before ovulation induction in anovulatory women with PCOS?
10a.CR – Semen analysis should be considered before starting ovulation induction treatment in infertile patients with PCOS and anovulation. ❖❖❖
10b.CR – Tubal patency testing should be considered on an individual basis before starting ovulation induction treatment in infertile patients with PCOS and anovulation. ❖❖❖

11.Are there add-on treatments to improve oocyte and endometrial quality in infertile women with PCOS?
11a.EBR – No specific add-on treatments should be considered to improve oocyte and endometrial quality in infertile women with PCOS. ❖❖❖⊕⊕◯◯

12.Could letrozole be administrated in combination with metformin?
12a.EBR – Letrozole could be considered in women with PCOS under metformin administration. ❖❖⊕◯◯◯

13.Should all the PCOS diagnostic criteria be assessed in the PCOS infertile patient?
13a.PP - The assessment of all the diagnostic criteria of PCOS could be beneficial for optimizing counselling and management infertile patients with PCOS. AMH could be useful in infertility setting for driving specific strategies of treatment.

14.Are progestins administration useful for inhibiting the LH surge in women with PCOS undergoing IVF cycles?
14a.EBR – In IVF cycles, where freeze-all protocol (also called "cycle segmentation") is planned, the administration of progestins could be considered to inhibit the LH surge, potentially reducing the costs. ❖❖⊕◯◯◯

The legend for the graphical description and the terminology used is extensively reported in Table 1. EBR: evidence-based recommendations, evidence sufficient to inform a recommendation made by the guideline development group. CR: consensus recommendations, in the absence of adequate evidence, a consensus recommendation has been made by the guideline development group, also informed by evidence from the general population. PP: practice points, evidence not sought; a practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or consensus recommendations

AMH Anti-Mullerian hormone, *CC* Clomiphene citrate, *LH* Luteinizing hormone, *IUI* Intrauterine insemination, *IVF* In vitro fertilization, *PCOS* Polycystic ovary syndrome

further new items were included and extrapolated from the same publication [3]. Eleven and 2 items were modified and deleted, respectively, from new recommendations included by the Working Group.

Following the revisions, a total of 93 recommendations were adapted from the PCOS International Guidelines [3]. A total of 14 new topics were analyzed, leading to the definition of 21 new clinically relevant recommendations (Table 2).

Finally, the Working Group sub-grouped all recommendations (integrating the new items to the main document) in specific sections (Table 3): 1. PCOS diagnosis, 2. preconception risk factors in PCOS (including the screening/diagnosis of PCOS-related comorbidities), 3. interventions for improving general and reproductive health in infertile women with PCOS, 4. general principles of infertility management in women with PCOS (including infertility assessment, drugs administration, complementary interventions/drugs), 5. treatment of PCOS-related anovulatory infertility (first-, second-, and third-line treatments), and 6. IVF in women with PCOS. An algorithm (Algorithm 1) for the management and treatment of infertile patients with PCOS has been implemented (Fig. 2).

The final document and Algorithm 1 are reported in Italian to prevent potential inaccuracies in translation, respectively in Supplementary Table 2 and Supplementary Fig. 1.

Discussion

Clinical guidelines are considered a valuable tool for enhancing the quality of care provided to patients. By consolidating evidence on specific topics, these guidelines facilitate clinicians in making timely, evidence-based decisions for their patients. They support the adoption of effective interventions while discouraging those that are ineffective or potentially harmful. Moreover, guidelines can enhance patient empowerment, shape public policy, standardize care practices, and inform the creation of performance measures and evaluations for diseases [18]. Additionally, clinical guidelines contribute to reducing healthcare costs by streamlining decision-making processes, minimizing unnecessary interventions, and promoting the efficient use of resources while maintaining high standards of care [18]. Evidence-based guidelines are indispensable for assisting physicians, policymakers, and patients across all medical fields, with particular significance in reproductive medicine. These general concepts on the need of clinical guidelines are particularly important for PCOS. In fact, PCOS is a condition with a considerable economic impact, in relation to the therapies needed to promote fertility in these patients [19]. Indeed, in about 50% of cases, PCOS patients do not achieve a pregnancy requiring to be scheduled for IVF programs [7, 12].

Despite these premises, few specific documents have been produced about the management of PCOS-related infertility [11, 12, 20], whereas many others focused on PCOS management included only brief sections on ovulation induction in this clinical contest [21–24]. In 2019, the International PCOS Network produced a specific document of evidence-based recommendations regarding the assessment and treatment of infertility in patients with PCOS [25]. More recently, an updated document on all clinical aspects of PCOS was published [3]. A specific section was dedicated to the management of infertility in women with PCOS [3]. The critical analysis of these documents suggests that, over the last few years, evidence-based medicine has driven new approaches for treating infertility in patients with PCOS, changing rapidly and deeply the clinical practice [12].

The need to translate and adapt international guidelines to each regional context has already been expressed by the authors themselves, to close the knowledge-practice gap, guide future research and enhance positive impact on the health of women with PCOS [26]. However, this wish has not always been fulfilled and national scientific societies have simply adopted these guidelines by providing a summary of them from a local perspective [27, 28]. Considering the absence of guidelines adapted to the Italian context for infertility in PCOS [10], SIRU and CECOS Italy decided to produce an official document for the diagnosis and management of infertility in women with PCOS following a methodology already adopted for the realization of the “2024 SIRU NICE-adapted guidelines” [10]. Simply providing a lay summary or referring to the original guideline is in our opinion a lost opportunity. A formal adaptation of the guidelines to the local context is a stronger and wiser approach.

Current paper provides a detailed account of the process involved in adapting to the Italian context the recommendations included in the "2023 International Evidence-based Guideline for the Assessment and Management of PCOS" related to infertility diagnosis and management (section number five of the original document [3]), which resulted to have the highest AGREE II score after our research and evaluation. A methodological process clinically important to produce the Italian Guidelines was to define other recommendations not reported in the section dedicated to the clinical management of infertile patients with PCOS if considered relevant for making complete the new document. After the first phase of adaptation of international recommendations and drafting of new ones, they were subjected to another two phases of revision. The first regarded the inclusion of new recommendations considered clinically

Table 3 Final document from the SIRU and the CECOS Italy on the diagnosis and management of infertility in patients with PCOS in Italy including published/adapted and new recommendations after integration of the comments/suggestions from public consultation and international experts

1. PCOS diagnosis

1.1 General principles

1.1.1 EBR – The diagnosis of polycystic ovary syndrome (PCOS) should be based on the presence of at least two of the following three criteria: (a) clinical and/or biochemical hyperandrogenism, (b) polycystic ovarian morphology (PCOM), and (c) irregular menstrual cycles, after exclusion of other causes of hyperandrogenism and/or irregular menses. ❖❖❖⊕⊕⊕◯

1.1.2 PP - The assessment of all the diagnostic criteria of PCOS could be beneficial for optimizing counselling and management infertile patients with PCOS. Anti-Mullerian hormone (AMH) could be useful in infertility setting for driving specific strategies of treatment.

1.2 Irregular cycles and ovulatory dysfunction

1.2.1 CR –Irregular menstrual cycles are defined as 3-year post menarche to perimenopause less than 21 or more than 35 days or less than 8 cycles per year ❖❖❖❖

1.2.2 CR – Ovulatory dysfunction should be confirmed by measuring serum progesterone levels 7 days before expected menses in the cycle in infertile patients with PCOS, even if menstrual cycles appear normal. A cut-off value of 5 ng/mL for serum progesterone levels could be considered to determine ovulation ❖❖

1.3 Biochemical hyperandrogenism

1.3.1.1 EBR - Healthcare professionals should use total testosterone and sex hormone binding globulin (SHBG) to assess biochemical hyperandrogenism as free androgen index (FAI, total testosterone × 100 / SHBG). ❖❖❖❖ ⊕◯◯◯

1.3.1.2 CR - In obese patients, free testosterone measurement should be preferred to FAI to assess biochemical hyperandrogenism. ❖❖❖

1.3.2 EBR - If FAI is not elevated, healthcare professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), recognizing their lower specificity and age-related decline in DHEAS levels. ❖❖❖ ⊕◯◯◯

1.3.3 EBR - Laboratories should use validated, highly accurate tandem mass spectrometry (LC-MS/MS) assays for measuring total testosterone and if needed, for androstenedione and DHEAS. Free testosterone should be assessed by calculation, equilibrium dialysis, or ammonium sulfate precipitation. ❖❖❖❖ ⊕⊕◯◯

1.3.4 EBR - Direct immunoassays (eg, radiometric and enzyme linked) for assessing total or free testosterone have limited accuracy and demonstrate poor sensitivity and precision for diagnosing hyperandrogenism in PCOS. ❖❖❖❖ ⊕⊕◯◯

1.3.5 PP – Other causes of hyperandrogenaemia, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis, iatrogenic causes, and syndromes associated with severe insulin resistance, should be excluded.

1.4 Clinical hyperandrogenism

1.4.1 EBR - The presence of hirsutism should be considered predictive of biochemical hyperandrogenism and PCOS in adults. ❖❖❖ ⊕◯◯◯

1.4.2 EBR - Healthcare professionals could recognize that female pattern hair loss and acne in isolation (without hirsutism) are relatively weak predictors of biochemical hyperandrogenism. ❖❖❖⊕◯◯◯

1.4.3 CR – A modified Ferriman Gallwey score (mFG) of 4–6 should be used to detect hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment. ❖❖❖❖

1.4.4 PP – Healthcare professionals should:
• Consider the Ludwig or Olsen visual scales for assessing female pattern hair loss.
• Note that there are no universally accepted visual instruments for assessing the presence of acne.
• Recognize that women commonly treat clinical hyperandrogenism cosmetically, diminishing their apparent clinical severity.
• Note that only terminal hairs need to be considered in defining hirsutism, and these can reach >5mm if untreated, vary in shape and texture, and are generally pigmented.
• Note that new-onset severe or worsening hyperandrogenism, including hirsutism, requires further investigation to rule out androgen-secreting tumors and ovarian hyperthecosis.

1.5 Ultrasound and PCOM

1.5.1 EBR - Follicle number per ovary (FNPO) should be considered the most effective ultrasound marker to detect PCOM in adults. ❖❖❖❖ ⊕⊕◯◯

1.5.2 EBR – FNPO, follicle number per cross-section (FNPS) and ovarian volume (OV) should be considered accurate ultrasound markers for PCOM in adults. ❖❖❖❖ ⊕⊕◯◯

1.5.3 CR – PCOM criteria should be based on follicle excess (FNPO) and/or ovarian enlargement. ❖❖❖❖

1.5.4 CR - FNPO ≥ 20 in at least 1 ovary should be considered the threshold for PCOM in adults if transducer band-width frequency > 8 MHz are used for ultrasonography. ❖❖❖❖

1.5.5 CR – OV >10ml or FNPS >12 in at least one ovary should be considered the threshold for PCOM if transducer band-width frequency < 8 MHz are used for ultrasonography or if image quality is insufficient to allow for an accurate assessment of follicle counts throughout the entire ovary. ❖❖❖❖

1.5.6 PP – If acceptable to the individual, the transvaginal approach is the most accurate for the diagnosis of PCOM.

Table 3 (continued)

1.5.7 PP – There is a need for training in careful and meticulous follicle counting per ovary and clear standardized protocols are recommended for PCOM reporting on ultrasound including at a minimum:
• Last menstrual period (or stage of cycle).
• Transducer band width frequency.
• Approach / route assessed.
• Total number of 2–9 mm follicles per ovary.
• Measurements in three dimensions (in cm) or volume of each ovary.
• Other ovarian features and / or pathology including ovarian cysts, corpus lutea, dominant follicles (10mm) (which should not be included in ovarian volume calculations).
• Reliance on the contralateral ovary FNPO for diagnosis of PCOM, where a dominant follicle is noted.
• Uterine features and / or pathology including endometrial thickness and pattern.

2. Preconception risk factors in PCOS

2.1 Cardiovascular disease risk

2.1.1 EBR – Women with PCOS should be considered at increased risk of cardiovascular disease and potentially of cardiovascular mortality. ❖❖❖⊕◯◯◯

2.1.2 EBR – All infertile women with PCOS should be assessed for cardiovascular disease risk factors. ❖❖❖❖⊕◯◯◯

2.1.3 CR – All infertile women with PCOS, regardless of age and body mass index (BMI), should have a lipid profile (cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level) at diagnosis. ❖❖❖❖

2.1.4 CR – All infertile women with PCOS should have blood pressure measured ❖❖❖❖

2.2 Impaired glucose tolerance and type 2 diabetes risk

2.2.1 EBR – Women with PCOS, regardless of age and BMI, have an increased risk of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes. ❖❖❖❖⊕⊕◯◯

2.2.2 EBR – Glycemic status should be assessed at diagnosis in all infertile patients with PCOS. ❖❖❖❖

2.2.3 EBR – All infertile women with PCOS should undergo a 75-g oral glucose tolerance test (OGTT). ❖❖❖❖⊕◯◯◯

2.3 Endometrial hyperplasia and cancer

2.3.1 EBR – Health care professionals should be aware of the increased risk of endometrial hyperplasia and cancer in premenopausal women with PCOS. ❖❖❖❖⊕◯◯◯

2.3.2 PP – When excessive endometrial thickness is detected, consideration of a biopsy with histological analysis and withdrawal bleed is indicated.

2.3.3 CR – Hysteroscopic assessment should not be considered as routinary evaluation for diagnostic work-up in infertile patients with PCOS. ❖

2.3.4 CR - Hysteroscopic assessment should be considered in infertile women with PCOS according to clinical data and ultrasonographic findings in consideration of the higher risk of endometrial premalignant/malignant diseases. ❖❖❖

2.4 Depression and anxiety

2.4.1 EBR – Healthcare professionals should be aware of the high prevalence of moderate to severe depressive symptoms and infertile women with PCOS should be screened for depression during psychological counselling for infertility work-up. ❖❖❖❖⊕⊕⊕⊕

2.4.2 EBR – Infertile women with PCOS should be screened for anxiety during psychological counselling for infertility work-up. ❖❖❖❖⊕⊕⊕⊕

2.4.3 CR – If moderate or severe depressive or anxiety symptoms are detected, practitioners should further assess, refer appropriately, or offer treatment. ❖❖❖❖

2.5 Psychosexual function

2.5.1 CR – Healthcare professionals could consider the multiple factors that can influence psychosexual function in PCOS including higher weight, hirsutism, mood disorders, infertility and PCOS medications. ❖❖❖

2.6 Eating disorders

2.6.1 EBR – Eating disorders and disordered eating should be considered, regardless of weight, in all infertile patients with PCOS. ❖❖❖⊕⊕◯◯

3. Interventions for improving general and reproductive health in infertile women with PCOS

3.1 Lifestyle management

3.1.1 EBR – Lifestyle intervention (exercise alone or multicomponent diet combined with exercise and behavioral strategies) should be recommended for all women with PCOS, especially for infertile patients, for improving metabolic health including central adiposity and lipid profile. ❖❖❖❖⊕◯◯◯

3.1.2 CR – Healthy lifestyle behaviors encompassing healthy eating and/or physical activity should be recommended in all infertile patients with PCOS to optimize general health, quality of life, body composition and weight management (maintaining weight, preventing weight gain and/or modest weight loss). ❖❖❖❖

3.2 Behavioral strategies

3.2.1 CR – Lifestyle interventions could include behavioral strategies such as goal-setting, self-monitoring, problem solving, assertiveness training, reinforcing changes, and relapse prevention, to optimize weight management, healthy lifestyle and emotional wellbeing in all infertile patients with PCOS. ❖❖❖

Table 3 (continued)

3.3 Dietary intervention

3.3.1 EBR – There is no evidence to support anyone type of diet composition over another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes. ❖❖❖⊕◯◯◯

3.3.2 CR – Any diet composition consistent with population guidelines for healthy eating will have health benefits and, within this, healthcare professionals should advise sustainable healthy eating tailored to individual preferences and goals. ❖❖❖❖

3.4 Exercise intervention

3.4.1 EBR - There is a lack of evidence supporting any one type and intensity of exercise being better than another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes. ❖❖❖⊕◯◯◯

3.5 Anti-obesity pharmacological agents

3.5.1 CR - Anti-obesity medications including liraglutide, semaglutide, tirzepatide, both glucagon-like peptide-1 (GLP-1) receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of obesity in infertile patients with PCOS before starting a reproductive program.❖❖❖

3.5.2 CR - We recommend using anti-obesity agents in PCOS only before starting a reproductive program.

3.5.3 PP - Effective contraception is needed in women with PCOS under GLP-1 receptor agonists administration until their discontinuation and before infertility treatment, as pregnancy safety data are lacking.

3.6 Anti-androgen pharmacological agents

3.6.1 PP - All infertile patients with PCOS should stop anti-androgen agents before starting a reproductive program.

3.7 Inositol

3.7.1 EBR - Inositol exerts limited clinical benefits including ovulation and body weight loss in infertile patients with PCOS. ❖❖❖⊕◯◯◯

3.7.2 EBR - Inositol in any form alone, or in combination with other therapies, should be considered experimental in women with PCOS-related infertility. The benefits and risks remain too uncertain to recommend inositol as a fertility treatment. ❖❖❖ ⊕◯◯◯

3.7.3 PP - There is limited evidence with uncertain results, on the effect of inositol on ovulation, clinical pregnancy, and live birth rates.

3.7.4 PP – The side effects and safety profile of inositol are currently unknown.

3.7.5 PP - Women should be informed that these agents can have limited regulation with variable dose, quality, consistency, and possible combination with other agents.

3.8 Bariatric/metabolic surgery

3.8.1 CR - Bariatric/metabolic surgery could be considered to improve weight loss, hypertension, diabetes (prevention and treatment), hirsutism, irregular menstrual cycles, ovulation, and pregnancy rates in severely obese patients with PCOS before to start a reproductive program. ❖❖❖

3.8.2 CR - Infertile patients with PCOS who underwent a bariatric/metabolic surgery can start a reproductive program only after achieving stable weight, usually one-year post-surgery, to minimize significantly increased risk of growth restriction, prematurity, small for gestational age, pregnancy complications, and prolonged hospitalization of the infant. ❖❖❖❖

3.9 Pregnancy outcomes

3.9.1 EBR – Women with PCOS are at higher risk for pregnancy complications, and an appropriate counselling should be provided to all infertile patients with PCOS. ❖❖❖❖⊕◯◯◯

3.9.2 EBR –Pregnant women with PCOS have an increased risk of gestational weight gain, miscarriage, gestational diabetes, hypertension in pregnancy and preeclampsia, intrauterine growth restriction, small for gestational age babies and low-birth weight, preterm delivery, and Caesarean section. ❖❖❖❖⊕◯◯◯

4. General principles of infertility management in women with PCOS

4.1 Premises

4.1.1 PP - The strategy for the management and treatment of infertile patients with PCOS should be guided by the reported algorithm (Algorithm 1).

4.1.2 PP - Those with PCOS should be reassured that pregnancy can often be successfully achieved either naturally or with assistance.

4.1.3 PP - Prenatal vitamin supplementation should be commenced with ovulation induction therapy aligned to routine preconception care.

4.1.4 PP - Pregnancy should be ruled out before initiating ovulation induction therapy.

4.1.5 PP - The use of letrozole and metformin is off-label in Italy. However, these medications may be considered after discussing the evidence, potential concerns, and side effects with the patient.

4.1.6 PP – Any potential congenital anomalies should be reported to the Italian Drug Agency.

4.2 Preconception risk factors

4.2.1 EBR - Women with PCOS should be counselled on the adverse impact of excess weight on clinical pregnancy, miscarriage, and live birth rates, following infertility treatment. ❖❖❖❖ ⊕◯◯◯

4.2.2 CR - Consistent with routine preconception care, in women with PCOS planning pregnancy, weight, blood pressure, smoking, alcohol, diet and nutritional status, folate supplementation (higher dose in those with BMI > 30 kg/m2), exercise, sleep, and mental, emotional, and sexual health should be considered and optimized to improve reproductive and pregnancy outcomes and overall health. ❖❖❖❖

4.2.3 PP - A healthy lifestyle, the prevention of excess weight gain, and the optimization of the preconception risk factors are needed before starting a reproductive program.

Table 3 (continued)

4.2.4 PP - The body weight and the height should be measured, and BMI calculated for all infertile patients with PCOS at initial visit.

4.2.5 PP – Comorbidities, such as diabetes, high blood pressure, anxiety, depression, and other mental health conditions, should be screened and optimally managed. All infertile patients with PCOS should be counselled regarding the risk of adverse pregnancy outcomes.

4.2.6 EBR – No specific add-on treatments should be considered to improve oocyte and endometrial quality in infertile women with PCOS. ❖❖❖⊕⊕◯◯

4.3 Preliminary analyses

4.3.1 CR – Semen analysis should be considered before starting ovulation induction treatment in infertile patients with PCOS and anovulation. ❖❖❖

4.3.2 CR – Tubal patency testing should be considered on an individual basis before starting ovulation induction treatment in infertile patients with PCOS and anovulation. ❖❖❖

5. Treatment of PCOS-related anovulatory infertility

5.1 Ovulation induction treatment

5.1.1 PP – Before considering an intrauterine insemination (IUI) or in vitro fertilization (IVF) program, a total of 6-12 ovulatory cycles should be completed according to clinical context, risks, benefits, costs, timing and patient's individual preferences. Consider a period of 6 ovulatory cycles for women older than 35 years.

5.1.2 PP – Women with PCOS who did not achieve a pregnancy after 12 ovulatory cycles should be considered as patients with unexplained infertility, considering treatment options in relation to clinical context, risks, benefits, costs, timing and patient's individual preferences.

5.1.3 EBR – After pregnancy exclusion, oral ovulation inductors could be administered without progesterone-induced uterine bleeding. ❖❖⊕◯◯◯

5.2 Letrozole

5.2.1 EBR - Letrozole should be the first-line pharmacological treatment for ovulation induction in infertile anovulatory women with PCOS, with no other infertility factors. ❖❖❖❖ ⊕⊕⊕⊕

5.2.2 EBR - Letrozole should be used rather than clomiphene citrate (CC) in women with PCOS with anovulatory infertility. ❖❖❖❖ ⊕◯◯◯

5.2.3 CR - Letrozole should be administered in an escalation regimen, starting from lowest to the highest doses (from 2.5 mg to 7.5 mg daily) for five days, starting in the early proliferative phase (2^{nd} - 3^{rd} day of the menstrual cycle). ❖❖❖

5.2.4 PP – Letrozole resistance should be diagnosed when 7.5 mg daily of letrozole for 5 days is ineffective to induce ovulation.

5.2.5 PP – Letrozole failure should be diagnosed when reproductive failure occurs after 6 ovulatory cycles.

5.2.6 EBR – Letrozole could be considered in women with PCOS under metformin administration. ❖❖⊕◯◯◯

5.2.7 PP - The use of letrozole for ovulation induction is off-label in Italy and other ovulation induction agents could be used.

5.3 CC

5.3.1 CR - CC should be administrated using an escalation regimen, starting from lowest up to highest doses (from 50 mg to 150 mg daily) for five days, starting in the early proliferative phase (2^{nd} - 3^{rd} day of the menstrual cycle). ❖❖❖

5.3.2 PP – CC resistance should be diagnosed when 150 mg daily of CC for 5 days is ineffective to induce ovulation.

5.3.3 EBR - CC failure should be diagnosed in case of reproductive failure after 6 ovulatory cycles. ❖❖❖⊕⊕◯◯

5.3.4 PP - Ovulation induction treatments with CC with or without metformin should be monitored to minimize the risk of multiple pregnancy.

5.4 Metformin

5.4.1 EBR - Metformin could be used alone in young (less than 30 years) women with PCOS with anovulatory infertility ❖❖❖ ⊕⊕◯◯

5.4.2 CR – Metformin is available as immediate- and extended-release formulation:
- immediate-release metformin could be taken at meals, beginning with 500 mg at dinner for 3–4 days, and then increasing by 500 mg every 3–4 days up to a maximal dosage of 2000 mg daily ❖❖
- extended-release metformin (1000 mg) could be taken with the evening meal and a second dose could be added after one week with breakfast up to a maximal dosage of 2000 mg daily. ❖❖

5.4.3.1 PP - Women should be counselled as to potential mild gastrointestinal side-effects with metformin.

5.4.3.2 PP - Healthcare and resource burden including monitoring, travel, and costs are lower with metformin.

5.5 CC and metformin

5.5.1.1 EBR - CC could be used in preference to metformin in women with PCOS with anovulatory infertility ❖❖❖ ⊕⊕◯◯

5.5.1.2 PP - The risk of multiple pregnancies is increased with CC use (alone or in combination with metformin), and therefore, CC should require ultrasound monitoring.

5.5.2 EBR - CC combined with metformin could be used rather than CC alone in women with PCOS with anovulatory infertility. ❖❖❖ ⊕⊕◯◯

5.5.3 EBR - CC combined with metformin could be used rather than metformin alone in women with PCOS with anovulatory infertility. ❖❖❖ ⊕⊕◯◯

5.6 Gonadotropins

5.6.1 EBR - Gonadotropins could be considered rather than the combination of CC and metformin in women with PCOS who are anovulatory and infertile with CC resistance and no other infertility factors. ❖❖❖ ⊕◯◯◯

5.6.2 EBR - Gonadotropins could be used in women with PCOS who are anovulatory and infertile, with CC and/or letrozole resistance and no other infertility factors. ❖❖ ⊕⊕◯◯

Table 3 (continued)

5.6.3 EBR - Gonadotropins could be second-line pharmacological therapy for women with PCOS who are anovulatory and infertile, with no other infertility factors and who have failed first line oral ovulation induction. ❖❖❖ ⊕⊕◯◯

5.6.4 PP - Where gonadotropins are to be prescribed, the following should be considered:
• Cost of the intervention for ovulation induction.
• Expertise required for the use of the intervention for ovulation induction.
• The degree of intensive ultrasound monitoring that is required.
• A low-dose step-up gonadotropin protocol should be used to optimize the chance of monofollicular development.
• Implications of potential multiple pregnancy.

5.6.5 PP - There appears to be no difference in the clinical efficacy of the available gonadotropin preparations.

5.6.6 CR – Ovulation induction with gonadotropin for non-IVF cycles should be strictly monitored to cancel cycles with a multiple follicular growth (more than two follicles) and minimize the risk of multiple pregnancy. ❖❖❖

5.6.7 PP - When using gonadotropins, cycles should be canceled if there are more than a total of 2 follicles greater than 14 mm in diameter for reducing the risk of multiple pregnancies, and patients should be advised to avoid unprotected intercourse.

5.7 Laparoscopic ovarian surgery

5.7.1 EBR - Laparoscopic ovarian surgery could be second-line therapy for women with PCOS who are anovulatory and infertile, with CC resistance and other potential infertility factors (such as endometriosis, fibroids, and so on). ❖❖❖ ⊕⊕◯◯

5.7.2 PP When using laparoscopic ovarian surgery, the following should be considered:
• Comparative cost of the intervention for ovulation induction.
• Expertise required for the safe use of the intervention for ovulation induction.
• Both intraoperative and postoperative risks, which are higher in women who are above healthy weight.

6. IVF in women with PCOS

6.1 General considerations

6.1.1 CR - IVF could be offered in women with PCOS and anovulatory infertility, if first- or second-line ovulation induction therapies have failed. ❖❖❖

6.1.2 PP - Women with PCOS undergoing IVF treatment should be counselled prior to starting treatment about the increased risk of ovarian hyperstimulation syndrome (OHSS) and strategies to reduce the risk should be offered.

6.2 Strategies for inhibiting luteinizing hormone (LH) surge

6.2.1 PP - The use of a gonadotropin releasing hormone (GnRH) antagonist protocol for women with PCOS undergoing IVF is recommended as it enables the use of GnRH agonist trigger, with the freezing of all embryos generated if required, reducing the risk of significant OHSS without compromising the cumulative live birth rate.

6.2.2 EBR – In IVF cycles, where freeze-all protocol (also called "cycle segmentation") is planned, the administration of progestins could be considered to inhibit the LH surge, potentially reducing the costs. ❖❖⊕◯◯◯

6.3 Trigger type

6.3.1 CR - Triggering final oocyte maturation with a GnRH agonist and freezing all suitable embryos are recommended, in an IVF cycle with a GnRH antagonist protocol, where a fresh embryo transfer is not intended or where there is an increased risk of OHSS. ❖❖❖❖

6.4 Choice of gonadotropin

6.4.1 CR - Either urinary or recombinant gonadotropin could be used in women with PCOS undergoing ovarian stimulation for IVF, with insufficient evidence to recommend a particular type of preparation. ❖❖❖

6.5 Exogenous LH

6.5.1 CR - Exogenous recombinant LH treatment should not be routinely used in combination with FSH therapy in women with PCOS undergoing controlled ovarian hyperstimulation for IVF. ❖

6.6 Adjunct metformin

6.6.1 EBR - Adjunct metformin therapy could be used before and/or during FSH ovarian stimulation in women with PCOS undergoing IVF treatment with GnRH agonist long protocol, to reduce the risk of developing OHSS and miscarriage. ❖❖❖ ⊕⊕◯◯

6.6.2 PP - If using metformin, the following could be considered:
• Commence metformin at the start of GnRH agonist treatment or before.
• Gradually titrate metformin up to a dose of between 1000 and 2500 mg daily in order to minimize side effects.
• Stopping metformin therapy at the time of the pregnancy test or period, unless the metformin therapy is otherwise indicated.

6.7 In vitro maturation (IVM)

6.7.1 EBR - IVM and intracytoplasmic sperm injection (ICSI) is associated with no risk of OHSS, but it has a lower cumulative live birth rate. ❖❖ ⊕⊕⊕◯

6.7.2 PP - IVM should only be considered in centers with adequate expertise. Advocacy is needed for regional or national centers specialized in this technique.

6.7.3 PP - IVM could be offered as an option in women with prior severe OHSS and where the risk of severe OHSS is deemed unacceptably high, provided that the center has expertise in IVM techniques.

6.7.4 PP - Evidence suggests that IVM/ICSI is less effective than standard IVF/ICSI in terms of clinical pregnancy per patient and live birth rate per patient.

The legend for the graphical description and the terminology used is extensively reported in Table 1. EBR: evidence-based recommendations, evidence sufficient to inform a recommendation made by the guideline development group. CR: consensus recommendations, in the absence of adequate evidence, a consensus recommendation has been made by the guideline development group, also informed by evidence from the general population. PP: practice points, evidence not sought; a practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or consensus recommendations

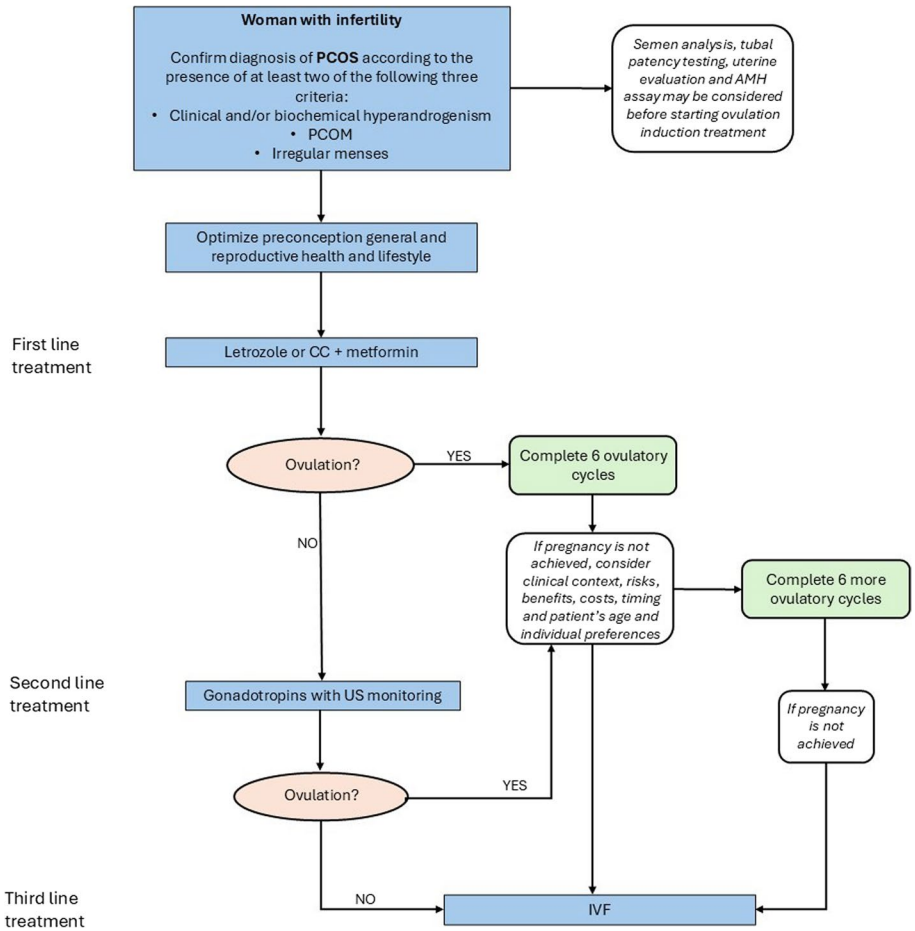

Fig. 2 (Algorithm 1). Strategy for the management and treatment of infertile patients with PCOS according to SIRU and CECOS Italy guidelines. AMH: anti-Mullerian hormone, CC: clomiphene citrate, IVF: in vitro fertilization, PCOM: polycystic ovarian morphology, PCOS: polycystic ovary syndrome, US: ultrasound

useful and lacking in the main referral document. The latter regarded external revisions using public consultation and international Referees. A public consultation was performed by external reviewers, including biologists, medical doctors (endocrinologists and gynecologists), midwives, psychologists, representatives of citizens, patients, and pharmaceutical and biomedical industries. On the other hand, two international Referees, experts in female infertility and in PCOS, revised all recommendations by making several suggestions and revisions, which were discussed by the SIRU-CECOS Working Group and integrated when considered relevant. After the revision process, the final document integrated adapted recommendations from the PCOS International Guidelines [3] and 21 new clinically relevant recommendations, subgrouped in specific sections (Table 3).

These guidelines present recommendations adapted from the 2023 International Guidelines for PCOS but differ in several key aspects. Firstly, the new recommendations are structured to be more practical, offering clinicians direct and tailored guidance based on specific patient conditions and clinical scenarios. This approach is particularly aligned with the characteristics of the Italian healthcare system. Secondly, they address gaps in the International Guidelines for PCOS, which left several clinical questions unresolved, by integrating insights from the latest Infertility Guidelines to provide more comprehensive recommendations [10]. Third, several specific aspects differentiate our document from the original referral document. For example, the approach to PCOS diagnosis. Here, we suggest evaluating all diagnostic criteria for PCOS in infertile patients, either because they are a negative prognostic factor for fertility, or to improve the counselling of the patient during preconceptional phase and pregnancy. We emphasize the importance of assessing anti-Müllerian hormone (AMH) levels in infertile patients with PCOS not as diagnostic criteria but to identify patients at high risk of ovarian

hyperstimulation syndrome (OHSS), treatment failure or multiple pregnancy. This assessment is particularly crucial prior to initiating a cycle of ovarian stimulation.

The assessment of OHSS risk is critical in determining the appropriate therapeutic strategy [12]. Emerging evidence suggests, for instance, that the use of follitropin delta may offer advantages for patients with elevated AMH levels, who are more likely to be high responders [29, 30]. However, the clinical trials conducted in this area primarily involved highly selected populations with favorable prognoses and high ovarian responses, limiting the generalizability of the findings to broader, unselected infertile populations [31]. Consequently, the Working Group did not reach a consensus to deviate from the recommendations of the International Guidelines [3]. Instead, it opted to maintain the guidance of not endorsing a specific gonadotropin for infertile patients with PCOS, leaving the decision to the clinician's discretion.

The recommendations of the PCOS International Guidelines left some unresolved issues and gaps that we tried to fill. For example, current guidelines tried to make clearer is the opportunity to assess the seminal and tubal factor before starting the therapy to induce ovulation in PCOS. It is now explicitly recommended that the seminal factor should always be assessed. We also recommend executing a tubal patency testing on an individual basis when the tube patency is not clear (i.e. in absence of previous pregnancies). In the referral document [3], the flowchart on which was based the management of infertility in the PCOS patient included a central pathway following best practice evidence, but also side indications that left wide discretion to the clinician. In particular, International Guidelines lacked clear directives on the number of therapeutic cycles to perform before declaring pharmacological failure, as well as criteria for deciding when to repeat the same treatment or to start an IVF program. To address these shortcomings, the Working Group synthesized widely accepted notions from clinical practice and formally incorporated them into these updated guidelines. We have therefore clearly indicated the protocols for letrozole, clomiphene citrate (CC) and metformin administration and detailed the definitions of CC- and letrozole-resistance and CC- and letrozole-failure. At the same time, we have chosen to advise how long to continue a treatment before moving on to the next one, while leaving the clinician the freedom to adapt this choice to the individual clinical context. The most recent evidence suggests a repeat of CC administration in relation to the anti-estrogenic effects of CC itself [32]. Endometrial thickness > 7 mm after six cycles of CC may suggest a repetition of another six cycles, rather than the transition to gonadotropins [32]. On the contrary, there is no evidence in the literature about the opportunity to use letrozole in the long term. However, the absence of antiestrogenic effects on the endometrium would suggest the possibility of continuation up to 12 cycles in younger patients [12].

Another controversial issue raised during the formal reviewing process was the use of AMH for infertile women with PCOS. Although AMH is considered by international guidelines as a biomarker of PCOM in adults, no cut-off level or commercial kit is recommended or suggested [3]. In addition, serum AMH levels have a large variability closely dependent on the patient's BMI and age [33]. Therefore, the decision to exclude AMH from the diagnostic criteria, as reflected in current guidelines, is a cautious approach due to the variability of AMH values, and lack of standardized values and kits. On the other hand, the evaluation of AMH levels may be crucial to personalize the treatment strategy of patients with PCOS in an infertility setting [34].

The strengths of these guidelines lie not only in the practical recommendations but also in the methodology employed. The adaptive framework of the International Guidelines enabled the development of updated, tailored, and high-quality recommendations without requiring substantial financial or human resource investments. The work was further enhanced by contributions from a specialized expert group on PCOS and fertility, supplemented by a transparent public consultation that engaged a diverse range of professionals and the input of two independent international experts. Nonetheless, we recognize certain limitations that remain. Overall, the quality of evidence in PCOS research is frequently low to moderate. Further studies are required to provide more definitive and clear guidance for the clinical management of infertile patients with PCOS, addressing the gaps currently left to clinician discretion. Secondly, the adaptability of these guidelines to the Italian healthcare context is constrained by significant regional disparities. Assisted reproductive technologies (ART) procedures are currently covered only in specific infertility centers within certain regions, limiting the uniform application of these guidelines across the country. While the SIRU-CECOS Italy guidelines may be relevant in regions that provide ART services, they may not be applicable in regions where such services are unavailable. Additionally, Italy has more private ART centers than public ones, and most of these facilities lack cryopreservation capabilities (https://w3.iss.it/site/RegistroPMA/PUB/Centri/CentriPma.aspx). However, the Italian government recently recognized ART as an essential healthcare service, mandating all regions to provide access to it for citizens starting January 1, 2024. This policy change will likely enhance the applicability of these guidelines. Nevertheless, a significant challenge

that remains to be addressed at the politic level is the prolonged waiting times for accessing ART services through the national healthcare system.

In conclusion, the current document now represents for SIRU and CECOS Italy the formal Italian guidelines for diagnosis and treatment of infertility in women with PCOS, and it replaces the section about the ovulatory dysfunctions included in the NICE-adapted guidelines from the SIRU for the diagnosis and management of infertility in Italy [10].

Abbreviations

AGREE II	Appraisal of Guidelines for Research and Evaluation II
AIOM	Italian Association of Medical Oncology
AMH	Anti-mullerian hormone
ARTs	Assisted reproductive technologies
ASRM	American Society of Reproductive Medicine
C C	Clomiphene citrate
CECOS	Centers for the Study and Conservation of Eggs and Sperm
CNEC	National Center for the Clinical Excellence, Quality and Safety of the Care
EtD	Evidence to Decision
GIMBE	Italian Team for the Evidence-Based Medicine
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICSI	Intracytoplasmic sperm injection
IUI	Intrauterine insemination
IVF	In vitro fertilization
MMWG	Multidisciplinary and Multiprofessional Working Group
NICE	National Institute of Clinical Excellence
PCOS	Polycystic ovary syndrome
PDTA	Diagnostic-Therapeutic-Care Pathways
PICO	Population, Intervention, Comparison and Outcomes
SIRU	Italian Society of Human Reproduction
SNLG	National System Guidelines System

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-025-01372-5.

Supplementary Material 1: Table 1. [All items selected and extracted by the SIRU-CECOS Italy Working Group from the 2023 International Evidence-based Guideline for the Assessment and Management of PCOS [3]. All original items were analyzed by the SIRU-CECOS Italy Working Group for relevance and applicability to the Italian context and contextualized to adult infertile women. In the table are reported the words/statements deleted and those changed in *italics*.]

Supplementary Material 2: Table 2. [SIRU-CECOS Italy guidelines for the diagnosis and treatment of infertility in women with PCOS – Italian version.]

Supplementary Material 3: Figure 1. [Strategy for the management and treatment of infertile patients with PCOS according to SIRU and CECOS Italy guidelines – Italian version.]

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SIRU – CECOS Working Group on Italian Guideline for Diagnosis and Treatment of Infertility in Women with PCOS

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Authors' contributions

S.P., A.G., and E.S. conceptualized and designed the study. S.P., G.S. and E.S. drafted the article. All authors (S.P., G.S., F.T., A.M., G.M., D.B., E.P., G.R., A.A., A.A., A.G., E.S.) interpreted the data, critically revised the article, provided their final approval of the version to be published, and agreed to be accountable for all aspects of the work, especially regarding its accuracy and integrity.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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