

PERSONALIZED METHODS TO THE MANAGEMENT OF WOMEN WITH POLYENDOCRINE METABOLIC OVARIAN SYNDROME IN THE PRESENCE OF INFERTILITY

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<https://doi.org/10.5281/zenodo.23363771>

Abstract. Polyendocrine metabolic ovarian syndrome (PMOS) is a common endocrine condition in women of reproductive age and a leading cause of anovulatory infertility. Its clinical and metabolic heterogeneity necessitates an individualized treatment strategy.

Personalized management should take into account the PMOS phenotype, metabolic profile, ovarian reserve, age, duration of infertility, and reproductive priorities.

Objective. To systematize and analyze current evidence on PMOS phenotyping and personalized strategies for the diagnosis and treatment of infertility associated with anovulatory dysfunction.

Materials and methods. An analytical literature review was conducted using PubMed, Scopus, Web of Science, Google Scholar, and the Cochrane Library, with additional manual screening of relevant reference lists. A total of 151 records were identified; after duplicates were removed, 124 records were screened. Thirty-eight full-text publications were assessed, and 25 publications formed the core evidence base. Additional sources were used to contextualize selected recommendations.

Results. Contemporary infertility management in PMOS is based on sequential assessment of the clinical phenotype, metabolic status, and reproductive prognostic factors.

Lifestyle modification is an important component of care for patients who are overweight or have obesity. Letrozole is considered the first-line medication for ovulation induction in anovulatory infertility associated with PMOS. Metformin is used according to the patient's metabolic profile. If oral induction is unsuccessful, gonadotropins or surgical management may be considered in carefully selected patients. In assisted reproductive technology (ART), prevention of ovarian hyperstimulation syndrome (OHSS) is particularly important.

Keywords: polyendocrine metabolic ovarian syndrome; PMOS; infertility; anovulation; personalized medicine; ovulation induction; letrozole.

INTRODUCTION

PMOS should be considered not only as a disorder of ovulation but also as a condition associated with changes in metabolic and vascular profiles. This is particularly important when pregnancy is planned, because the baseline severity of metabolic abnormalities may determine whether the woman's health should be optimized before active infertility treatment begins. At the same time, the reproductive goal should not be postponed without clinical justification; the timing of transition between treatment stages should be individualized.

Polyendocrine metabolic ovarian syndrome (PMOS) is a heterogeneous endocrine and metabolic condition characterized by varying combinations of ovulatory dysfunction, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology. PMOS is one of the most common endocrine disorders in women of reproductive age [1,7] and is a leading cause of anovulatory infertility.

However, clinical manifestations vary considerably: some patients predominantly have reproductive symptoms, whereas others have pronounced metabolic abnormalities. Therefore, the diagnosis alone is insufficient to determine an appropriate treatment strategy.

According to current international recommendations, PMOS is diagnosed in adults when at least two of the following three features are present, after other causes have been excluded: clinical and/or biochemical hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology [1]. In adult women, anti-Müllerian hormone (AMH) may be used within an appropriate diagnostic algorithm as an alternative to ultrasound assessment of ovarian morphology, but it should not be used as a stand-alone diagnostic test [1].

Thus, the contemporary approach to infertility associated with PMOS is shifting from a uniform treatment regimen toward a sequential, phenotype-oriented strategy.

AIM AND OBJECTIVES OF THE REVIEW

To systematize and analyze current evidence on phenotyping of polyendocrine metabolic ovarian syndrome (PMOS) and personalized strategies for diagnosing and treating infertility in women with anovulatory infertility associated with polycystic ovary syndrome.

MATERIAL AND METHODS

Study design: analytical literature review. Additional sources [26–30] were used to contextualize selected points. This review addresses contemporary approaches to diagnosing and treating infertility in women with PMOS. Scientific publications were searched in PubMed, Scopus, Web of Science, Google Scholar, and the Cochrane Library. Additional manual searches were performed through the reference lists of relevant publications.

The stages of source selection according to PRISMA 2020 are presented in Table 1.

Stage of selection	Number of records
Records identified in electronic databases	142
Additional records identified through other sources	9
Records after removal of duplicates	124
Records excluded after title and abstract screening	86
Full-text publications assessed for eligibility	38
Publications excluded after full-text assessment	20
Publications included in the core qualitative evidence base	25
Additional sources used for contextualization	5

Note: PMOS = polyendocrine metabolic ovarian syndrome. Source: compiled by the authors.

As shown in Table 1, 142 publications were initially identified in electronic databases and 9 additional sources were found. After 27 duplicates were removed, 124 records remained.

Title and abstract screening excluded 86 publications. Thirty-eight publications underwent full-text assessment. Following full-text review, 20 publications were excluded; 25 publications formed the core evidence base for the qualitative analysis, while 5 additional sources were used to contextualize the recommendations and current approaches.

Inclusion criteria were publications addressing PMOS diagnosis and phenotyping, metabolic status, treatment of anovulatory infertility, and ART; clinical guidelines; systematic reviews; meta-analyses; and original studies.

Exclusion criteria were publications outside the subject of the review, studies that did not provide data on the diagnosis or treatment of infertility associated with PMOS, duplicate publications, and sources that did not allow the clinical significance of the data to be assessed.

Review limitations. The quantitative stages of publication selection are reported according to the original literature-selection scheme. Because the source materials did not provide exact search dates, publication languages, or search strings, these parameters were not reconstructed. This limits the reproducibility of the search strategy and should be considered when interpreting the findings.

RESULTS

An important practical principle is to distinguish the diagnostic phenotype from the treatment phenotype. Two patients may meet the criteria for the same diagnostic PMOS phenotype but differ substantially in age, body mass index (BMI), metabolic risk, duration of infertility, and ovarian response. Phenotyping should therefore serve as the starting point for risk stratification, after which the treatment strategy is adjusted according to individual prognostic characteristics.

When selecting an ovulation-induction method, clinicians should consider not only the probability of ovulation but also the likelihood of clinical pregnancy and live birth, the risk of multiple pregnancy, the need for monitoring, and treatment tolerability. The shift from assessing a single intermediate outcome to evaluating final reproductive outcomes explains the current preference for letrozole over clomiphene citrate [1,10].

The timing of transition from one treatment line to another also deserves attention.

Repeating ineffective treatment for too long may lead to an unjustified loss of reproductive time, particularly in patients of advanced reproductive age or with long-standing infertility. Conversely, premature escalation increases medication and procedural burden. The duration of each treatment stage should therefore be individualized.

During ovarian stimulation, personalization means dynamically adjusting treatment. The starting dose is only an initial reference point; subsequent decisions are based on the actual follicular response. This approach may reduce the likelihood of both an inadequate response and excessive stimulation, particularly in patients with signs of increased ovarian sensitivity [1,6].

DIAGNOSIS AND PHENOTYPING PMOS

In adult women, PMOS is diagnosed when at least two of three features are present—hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology—after alternative causes have been excluded [1].

According to the international consensus on polycystic ovary syndrome (ESHRE/ASRM, 2018; updated in 2023), four major disease phenotypes are distinguished, with substantial differences in metabolic risk and the severity of anovulatory infertility [1,2].

Phenotype	Hyperandrogenism	Ovulatory dysfunction	Polycystic ovarian morphology
A	Present	Present	Present
B	Present	Present	Absent
C	Present	Absent	Present
D	Absent	Present	Present

The most pronounced manifestations of metabolic syndrome and lower sensitivity to ovulation induction have been described predominantly in phenotypes A and B. At the molecular level, these patients may have abnormalities in post-receptor tyrosine phosphorylation of insulin receptor substrates (IRS-1, IRS-2), which impair GLUT-4 translocation and contribute to tissue-level disturbances in glucose utilization in the context of hyperandrogenism [13,20].

Phenotyping is one component of stratification, but it should not be the sole criterion for treatment selection. Treatment decisions should also account for the patient's individual reproductive and metabolic characteristics.

METABOLIC STATUS AND INSULIN RESISTANCE

Insulin resistance is an important pathophysiological component of PMOS. There is no single standardized test for its routine quantitative assessment in every patient; therefore, metabolic evaluation should include measures of carbohydrate and lipid metabolism as well as an overall cardiometabolic risk assessment.

Metabolic risk should be assessed independently of the formal phenotype. The presence of a particular phenotype does not reliably determine the severity of metabolic abnormalities in an individual patient. The evaluation and management plan should reflect the patient's actual clinical findings and reproductive plans.

ASSESSMENT OF REPRODUCTIVE PROGNOSIS

The choice of treatment depends on the nature of ovulatory dysfunction, the patient's age, BMI, metabolic abnormalities, duration of infertility, coexisting infertility factors, and outcomes of previous treatment. A contemporary strategy uses treatment methods sequentially and in a stepwise manner—from lifestyle modification to pharmacological ovulation induction and, if this is unsuccessful, to surgical methods or assisted reproductive technologies.

AMH measurement and antral follicle count provide additional information about ovarian characteristics and the expected response to stimulation. In patients with PMOS, a pronounced follicular response may be associated with an increased risk of OHSS [2,15].

Treatment selection is determined by the type of ovulatory dysfunction, age, BMI, metabolic abnormalities, duration of infertility, coexisting infertility factors, and the results of previous treatment. The principal factors guiding personalization are summarized in Table 3.

Lifestyle modification—including weight reduction where appropriate, dietary adjustment, and increased physical activity—is recognized as an initial component of care. It may improve metabolic parameters and ovulatory function, but lifestyle modification alone should not be regarded as a universal fertility-restoration treatment. It is a foundational component of management for patients who are overweight or have obesity [9,10]. Although it may improve metabolic and ovulatory outcomes, its direct effect on live birth is less consistent [15]. Lifestyle changes should therefore form part of comprehensive treatment rather than serve as a universal substitute for specific infertility therapy.

Metformin is used primarily to address metabolic abnormalities. It should not be considered a universal replacement for ovulation-induction medication; the decision to prescribe it should be based on the patient's metabolic profile [2].

If first-line oral ovulation induction is unsuccessful, gonadotropins may be considered [1]. Gonadotropins are used as a second-line treatment when letrozole, clomiphene citrate, or combined oral therapy is ineffective. Because patients with PMOS may have increased ovarian sensitivity to gonadotropin stimulation and a higher risk of multifollicular development, stimulation should use low-dose step-up protocols with careful ultrasound monitoring to minimize the risk of OHSS and multiple pregnancy.

Sequential use of letrozole followed by the addition of gonadotropins in cases of an insufficient follicular response has shown acceptable efficacy and safety in patients with PMOS who are resistant to clomiphene citrate monotherapy, according to a systematic review and meta-analysis.

Low-dose regimens and ultrasound monitoring allow treatment to be adapted to individual ovarian sensitivity. This sequential approach may be considered in selected patients, although further evaluation of its efficacy and safety is needed [16].

Laparoscopic ovarian drilling is a possible second-line option for carefully selected patients who are resistant to pharmacological ovulation induction [17]. Contemporary reviews indicate that ovulation may be restored after laparoscopic drilling, but they also emphasize the risk of a reduction in ovarian reserve, which should be considered when selecting this method [17].

During ART, prevention of an excessive ovarian response and OHSS is particularly important. The protocol and initial gonadotropin dose should be selected according to the patient's characteristics and the dynamics of ovarian response. In patients at increased risk of OHSS, an antagonist protocol, a GnRH agonist trigger, and a freeze-all strategy may be used when clinically indicated [1]. Luteal-phase support after ART should be provided according to the selected protocol and clinical circumstances.

Specific interventions intended to improve endometrial receptivity in PMOS do not yet have sufficient evidence to support routine use [19]. Glucagon-like peptide-1 receptor agonists should primarily be considered for weight management and reduction of metabolic risk; evidence is currently insufficient to support their routine use specifically to improve reproductive outcomes [1]. Bariatric surgery may be considered in selected patients with severe obesity as part of metabolic-risk management, with the timing of pregnancy planned individually.

Data-driven stratification of PMOS subtypes may improve prediction of treatment response, but further validation is required [21].

Practical algorithm for personalization

At the first stage, the diagnosis of PMOS is confirmed and alternative causes of hyperandrogenism and ovulatory dysfunction are excluded. At the second stage, all infertility factors affecting the couple are assessed. At the third stage, the metabolic profile and the need for its optimization are determined. At the fourth stage, a method of restoring ovulation or proceeding to ART is selected with consideration of age, duration of infertility, and expected ovarian response. After each stage, clinical outcomes and safety are assessed, and the treatment strategy is modified when necessary [5,15,22,23].

Factor	How it informs treatment personalization
Clinical phenotype	Helps characterize the combination of hyperandrogenism, ovulatory dysfunction, and ovarian morphology.
Age and duration of infertility	Inform the urgency of treatment and the time allowed for each treatment stage.
Metabolic profile	Guides lifestyle interventions and the use of medication for metabolic indications.
Ovarian reserve and expected response	Help tailor stimulation and assess the risk of an excessive ovarian response/OHSS.
Other infertility factors	Determine whether ovulation induction alone is appropriate or whether other treatments, including ART, should be considered.
Previous treatment response	Guides decisions about continuing, adjusting, or escalating treatment.

Discussion

The findings support a practical model of personalized care for patients with PMOS. The first level involves confirming the diagnosis and excluding disorders with a similar clinical presentation. The second level comprises assessment of the couple's reproductive profile: ovulatory pattern, age, duration of infertility, male and tubal factors, and the condition of the uterus and endometrium. The third level involves metabolic stratification. The fourth level concerns prediction of treatment response and selection of the most appropriate intervention, followed by reassessment of efficacy and safety.

A personalized approach does not mean performing the maximum number of diagnostic tests or prescribing the most complex treatment. Rather, its goal is to select the least intensive intervention that is sufficient and likely to provide the greatest clinical benefit. In a patient with anovulatory infertility and no other infertility factors, sequential ovulation induction is appropriate. If a male or tubal factor is identified, earlier transition to ART may be more rational.

In the presence of pronounced metabolic abnormalities, metabolic optimization may be needed alongside reproductive treatment, without unjustified postponement of the reproductive goal. An important feature of PMOS is that the clinical profile can change over time. Body weight, metabolic status, severity of hyperandrogenism, and reproductive goals may change.

Personalization should therefore not be a one-time procedure performed during the initial assessment. Risk factors and treatment efficacy should be reassessed after each significant stage of therapy [1,5,6]. A limitation of the evidence base is the shortage of studies directly comparing treatment outcomes across different PMOS phenotypes.

An emerging direction is the integration of clinical, hormonal, metabolic, and ultrasound data into prognostic models. In the future, such models may help estimate the likelihood of response to letrozole, the need for gonadotropins, the risk of an excessive response during ART, and the probability of live birth. Before these tools are introduced into practice, however, their reproducibility and clinical utility must be confirmed in independent cohorts [3,13,21,24].

The analysis indicates that infertility treatment in PMOS should not be based on a single disease feature. Instead, it should integrate the clinical phenotype, metabolic profile, age, duration of infertility, ovarian reserve, and other reproductive prognostic factors. The presence of PMOS does not automatically mean that anovulation is the only cause of infertility.

Personalization therefore begins with comprehensive assessment of the couple and identification of all clinically relevant infertility factors. Phenotyping is a tool for stratification, not a stand-alone algorithm for prescribing medication. Individual metabolic risk must be assessed independently of the formal phenotype.

The strongest evidence supports letrozole as the first-line medication for ovulation induction in anovulatory infertility associated with PMOS when no other infertility factors are present [2,11,12]. Metformin should be considered on the basis of metabolic indications rather than as mandatory treatment for every patient with PMOS [2].

Personalization is particularly important when gonadotropins and ART are used because of the risk of an excessive ovarian response and OHSS. The goal of stimulation is an adequate and safe response, not the maximum possible number of oocytes [1]. Laparoscopic ovarian drilling remains an option for carefully selected patients but should not be used routinely [18,19].

Promising metabolic and data-driven approaches require further study and external validation [2,3,25].

Thus, personalization in PMOS is a dynamic process: after each treatment stage, the diagnosis, infertility factors, metabolic status, and ovarian response should be reassessed, and the strategy should be adjusted when needed.

Conclusion

The practical value of a personalized approach lies in the ability to determine not only the first-line medication but also the optimal sequence of subsequent interventions, the duration of each stage, and the criteria for moving to the next line of treatment. This is particularly important for patients with combined reproductive and metabolic disorders. Contemporary treatment of infertility associated with PMOS should follow the principle of “the right treatment for the right patient at the right time,” with repeated assessment of efficacy and safety at every stage.

Infertility management in women with PMOS requires a comprehensive and individualized approach. Identification of the clinical phenotype and assessment of the metabolic profile, ovarian reserve, and other reproductive prognostic factors make it possible to adapt the treatment strategy to the individual patient. For anovulatory infertility associated with PMOS, letrozole is the first-line medication for ovulation induction. Metformin is of particular relevance for patients with appropriate metabolic indications. Gonadotropins, laparoscopic ovarian drilling, and ART should be considered according to individual clinical circumstances, previous treatment response, and safety considerations.

Personalized treatment of infertility in PMOS should be regarded as a dynamic process involving sequential assessment of the patient's clinical, metabolic, and reproductive characteristics, followed by adaptation of the treatment strategy.

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