

POLYENDOCRINE METABOLIC OVARIAN SYNDROME AND WOMEN'S HOLISTIC HEALTH: INTERFACES BETWEEN HORMONAL DYSFUNCTION, METABOLISM, AND FERTILITY

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Miriã Carvalho de Abreu¹, Victor Lucas Dutra de Moraes², Beatriz Jonas Francisconi³, Isadora Chiconelli Vanzo⁴, Raiane Mariah Roama Alves⁵, José Augusto Monteiro de Souza⁶, Cintya Dornel Queiroz⁷ and Josianne Barbosa Macedo⁸

Abstract

Polyendocrine Metabolic Ovarian Syndrome (PMOS) has manifestations that extend beyond the reproductive system, involving metabolic, inflammatory, intestinal, and cellular alterations. This study aimed to analyze the condition's main pathophysiological interfaces and their repercussions on ovarian function and women's quality of life. This qualitative, exploratory integrative literature review was

¹ Undergraduate Student in Biomedicine
Centro Universitário UNA

E-mail: micaabreu10@gmail.com
Lattes: <https://lattes.cnpq.br/8323570526869084>

² Undergraduate Student in Nursing
Faculdade Católica Imaculada Conceição do Recife (FICR)
E-mail: victorlucasmoraes30@gmail.com
ORCID: <https://orcid.org/0009-0007-9086-1400>

³ Medical Degree
Centro Universitário de Pinhais (FAPÍ)
E-mail: biaajonasfrancisc@gmail.com
ORCID: <https://orcid.org/0009-0004-3367-595X>

⁴ Medical Degree
Centro Universitário de Pinhais (FAPÍ)
E-mail: Isadoracvanzo@gmail.com
ORCID: <https://orcid.org/0009-0007-2826-754X>

⁵ Medical Degree
Centro Universitário de Pinhais (FAPÍ)
E-mail: raiane.mariah.3@gmail.com
ORCID: <https://orcid.org/0009-0000-4281-0077>

⁶ Undergraduate Medical Student
Centro Universitário São Lucas (Afya)
E-mail: jose.sza2002@gmail.com
ORCID: <https://orcid.org/0000-0001-6776-2104>

⁷ Undergraduate Student in Physical Therapy
Centro Universitário Tocantinense Presidente Antônio Carlos (AFYA)
E-mail: cintyadornel@gmail.com
Lattes: <http://lattes.cnpq.br/0864313338539020>

⁸ Postgraduate Degree in Cognitive Behavioral Therapy and Family Psychotherapy
CEUNI - FAMETRO
E-mail: jbm.josy@gmail.com
ORCID: <https://orcid.org/0009-0008-1148-318X>

conducted in the PubMed/MEDLINE, Scopus, Web of Science, and Embase databases and considered publications from 2021 to 2026. Following the identification, screening, and eligibility stages, 17 studies were included. The studies demonstrated relationships among insulin resistance, hyperandrogenism, gut dysbiosis, inflammation, and altered ovarian function. Mitochondrial alterations, NAD⁺ deficiency, and impaired communication between the oocyte and granulosa cells were also identified and associated with impaired follicular development and oocyte competence. Experimental and clinical studies further indicated potential effects of nutritional interventions, bioactive compounds, and microbiota-targeted strategies. Therefore, an integrated understanding of the mechanisms involved may support more individualized approaches to prevention and care that consider the condition's metabolic, reproductive, and psychosocial dimensions.

Keywords: Gut microbiota, Hyperandrogenism, Insulin resistance, Mitochondrial dysfunction, Quality of life.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS), traditionally understood from a gynecological and reproductive perspective, is now recognized as a complex, systemic condition of a metabolic-polyendocrine nature. Referred to by some authors as Polyendocrine Metabolic Ovarian Syndrome (PMOS), it is highly prevalent among women of reproductive age and is a major cause of chronic anovulation, hyperandrogenism, and infertility (Yu et al. 2023). Its manifestations are not limited to ovarian alterations but involve different physiological systems and processes, including insulin resistance, altered energy metabolism, chronic low-grade inflammation, and hormonal imbalances (Han et al. 2021). In this context, the gut microbiota has emerged as an important component of the condition's pathophysiology, since changes in its composition and activity can interfere with metabolic, hormonal, and immune regulation. The brain-gut-ovary axis has also been investigated for its role in communication among these systems and in maintaining reproductive and metabolic homeostasis (Liang et al. 2021).

The complexity of PMOS is related to the continuous interaction among its various pathophysiological components. Although the diagnostic criteria are based primarily on hyperandrogenism, ovulatory dysfunction, and ovarian morphology, these parameters do not encompass the full diversity of the syndrome's clinical and metabolic manifestations (Farhadi-Azar et al. 2022). Insulin resistance can stimulate ovarian androgen production, thereby contributing to the worsening of hyperandrogenism and metabolic alterations (Zhang et al. 2023). In parallel, an imbalance in the gut microbiota can influence glucolipid homeostasis, inflammation, and hormonal signaling, establishing a bidirectional relationship between the intestinal environment and ovarian function (Pratama et al. 2024). Within the follicular microenvironment, alterations in lipid metabolism, NAD⁺ availability, mitochondrial function, and communication between the oocyte and granulosa cells may impair follicular development and oocyte competence (Wang et al. 2021). These alterations reinforce the need to understand the syndrome beyond ovarian morphology by considering the integration of metabolic, endocrine, intestinal, and reproductive mechanisms (Qian et al. 2024).

The relevance of this study stems from the metabolic, reproductive, and psychosocial repercussions associated with the syndrome (Tabassum et al. 2021). An integrated understanding of PMOS may contribute to more comprehensive prevention, monitoring, and treatment strategies that consider women's health and quality of life.

Accordingly, the general objective of this study is to analyze, through an integrative literature review, the interfaces among hormonal, metabolic, intestinal, and ovarian alterations in PMOS and their repercussions on fertility and women's holistic health. Specifically, the study seeks to: a) analyze the relationship among hyperandrogenism, insulin resistance, and metabolic alterations; b) investigate the involvement of the gut microbiota in the gut-brain-ovary axis; c) understand the role of mitochondrial dysfunction and cellular alterations in the ovarian microenvironment; and d) discuss their repercussions on fertility, quality of life, and therapeutic possibilities.

METHODOLOGY

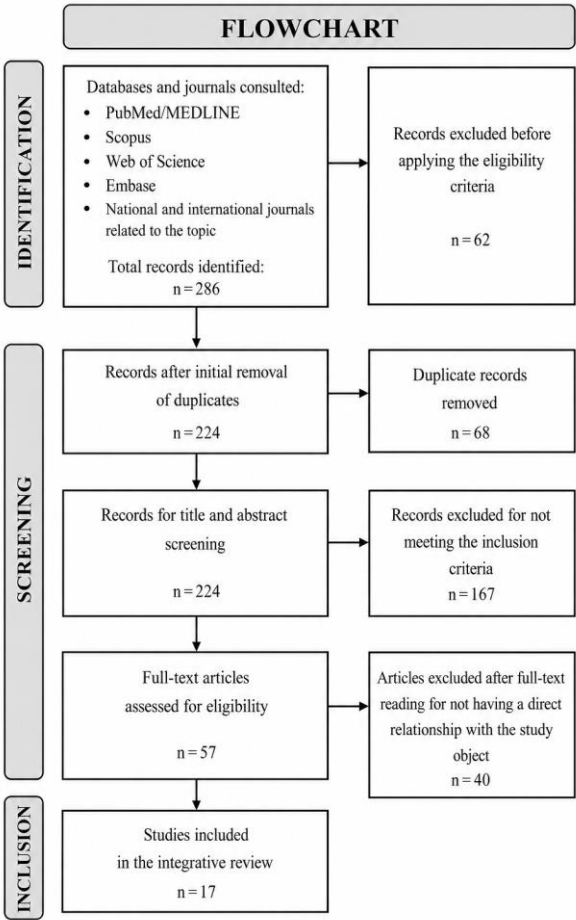
This is an integrative literature review with a qualitative, exploratory approach. The qualitative approach makes it possible to understand the different aspects and relationships present in the phenomenon under investigation (Gil, 2019). The guiding question was: What are the main metabolic, hormonal, and ovarian alterations associated with Polyendocrine Metabolic Ovarian Syndrome, and what are their repercussions on fertility and women's holistic health?

The literature search was conducted in the PubMed/MEDLINE, Scopus, Web of Science, and Embase databases, as well as in national and international journals, using descriptors and free-text terms exclusively in English related to Polycystic Ovary Syndrome, Metabolic Syndrome, Metabolism, Hyperandrogenism, Insulin Resistance, Gut Microbiota, Ovarian Function, and Fertility. The terms were combined using the Boolean operators AND and OR, according to the specific features of each database.

Scientific articles published between 2021 and 2026, in any language provided that they could be translated, were included if they were available in full text and directly related to the guiding question and objectives of this study. Duplicate articles, narrative reviews, studies of low relevance to the topic, papers published in conference proceedings, letters to the editor, publication reviews, and preprints were excluded. At the end of the selection process, 17 articles were included following the reading and assessment of their titles, abstracts, and full texts, as shown in Figure 1.

Figure 1

Flowchart of the article search, screening, eligibility, and selection process.



Source: Prepared by the authors (2026).

The studies were analyzed descriptively and interpretively to identify convergences, differences, and relationships among the findings. The content analysis method proposed by Bardin (2016) was used to organize and interpret the information, enabling the identification and grouping of the main themes found in the literature. Based on this analysis, the results were organized into three thematic axes: metabolic, hormonal, and polyendocrine interrelationships; integration among the microbiota, metabolism, and ovarian function; and repercussions on fertility, quality of life, and therapeutic possibilities.

RESULTS AND DISCUSSION

Seventeen articles were selected and organized alphabetically in Table 1, which presents the author(s) and year, title, objective, method, and main results of the studies analyzed.

Table 1

Characteristics of the selected studies

Author(s)/ year	Title	Objective	Method	Main results
Cao <i>et al.</i> (2022)	<i>Adipose mesenchymal stem cell-derived exosomal microRNAs ameliorate polycystic ovary syndrome by protecting against metabolic disturbances</i>	To investigate the effect of exosome-derived microRNAs from mesenchymal stem cells on metabolic alterations associated with PMOS.	Experimental study using an animal model of PMOS, with analysis of the exosomes and microRNAs involved in the metabolic alterations.	The exosomes exerted protective effects against metabolic alterations and contributed to improvements in characteristics associated with PMOS.
Chen <i>et al.</i> (2022)	<i>Resveratrol ameliorates polycystic ovary syndrome via transzonal projections within oocyte-granulosa cell communication</i>	To investigate the effect of resveratrol on communication between the oocyte and granulosa cells in PMOS.	Experimental study using an animal model of PMOS, transcriptomic analyses, PCR, Western blotting, phalloidin staining, and evaluation of human samples.	Resveratrol restored transzonal projections and communication between the oocyte and granulosa cells, promoting follicular development.
Cincione <i>et al.</i> (2021)	<i>Effects of mixed of a ketogenic diet in overweight and obese women with polycystic ovary syndrome</i>	To assess the effects of a ketogenic diet on anthropometric, metabolic, and hormonal parameters in women with PMOS and excess body weight.	Nonrandomized, single-arm intervention study involving 17 women who underwent the intervention for 45 days.	Reductions were observed in weight, BMI, waist circumference, fat mass, HOMA-IR, LH, the LH/FSH ratio, and testosterone, together with increases in FSH and SHBG.
Farhadi-Azar <i>et al.</i> (2022)	<i>The prevalence of polycystic ovary syndrome, its phenotypes and cardio-metabolic features in a community sample of Iranian population: Tehran</i>	To estimate the prevalence of PMOS and analyze its phenotypes and cardiometabolic characteristics.	Population-based cross-sectional study involving 1,960 women aged 18 to 45 years.	Prevalence varied according to the diagnostic criterion, and phenotypes involving hyperandrogenism displayed more pronounced adiposity and metabolic alterations.

	<i>Lipid and Glucose Study</i>			
Han <i>et al.</i> (2021)	<i>Androgen-induced gut dysbiosis disrupts glucolipid metabolism and endocrinal functions in polycystic ovary syndrome</i>	To investigate the relationship among androgen excess, gut dysbiosis, and metabolic and endocrine alterations in PMOS.	Experimental study involving rats with DHEA-induced PMOS, including analyses of the gut microbiota, metabolites, and metabolic and endocrine parameters.	Androgen excess promoted gut dysbiosis and alterations in glucolipid metabolism and endocrine functions.
Li, C. <i>et al.</i> (2021a)	<i>Eight-hour time-restricted feeding improves endocrine and metabolic profiles in women with anovulatory polycystic ovary syndrome</i>	To assess the effects of time-restricted feeding on metabolic and endocrine parameters.	Clinical intervention study involving women with anovulatory PMOS who followed a time-restricted feeding regimen.	The intervention improved the participants' metabolic and endocrine parameters.
Li, T. <i>et al.</i> (2021b)	<i>Tempol ameliorates polycystic ovary syndrome through attenuating intestinal oxidative stress and modulating of gut microbiota composition-serum metabolites interaction</i>	To investigate the role of intestinal oxidative stress and the microbiota in PMOS and assess the effect of Tempol.	Experimental study involving rats with PMOS, assessing ovarian function, glucose tolerance, oxidative stress, microbiota, and serum metabolites.	Tempol improved ovarian function and glucose tolerance, reduced oxidative stress, and modulated the gut microbiota.
Liang <i>et al.</i> (2021)	<i>Gut microbiota alterations reveal potential gut-brain axis changes in polycystic ovary syndrome</i>	To investigate alterations in the gut microbiota and their possible relationship with the gut-brain axis in PMOS.	Comparative observational study of the gut microbiota composition of women with PMOS and controls.	Alterations in gut microbiota composition associated with PMOS were identified, suggesting potential changes in the gut-brain axis.
Liao <i>et al.</i> (2022)	<i>Effects of androgen excess-related metabolic disturbances on granulosa cell function and follicular development</i>	To investigate the effects of androgen excess on granulosa cells and follicular development.	Experimental and translational study involving RNA-seq analysis, granulosa cells, and in vitro follicle culture.	Altered gene expression related to lipid metabolism, fatty acid synthesis, and steroidogenesis was identified and associated with impaired follicular development.
Pratama <i>et al.</i> (2024)	<i>Mechanism of elevated LH/FSH ratio in lean PCOS revisited: a path analysis</i>	To investigate the mechanisms associated with an elevated LH/FSH ratio in lean	Cross-sectional study involving 110 lean women with PMOS and using hormonal and	The results demonstrated relationships among neuroendocrine, metabolic, and hormonal

		women with PMOS.	metabolic assessments and path analysis.	factors associated with an elevated LH/FSH ratio.
Qian <i>et al.</i> (2024)	<i>Integrated lipid metabolomics and proteomics analysis reveal the pathogenesis of polycystic ovary syndrome</i>	To identify metabolic and protein alterations associated with the pathogenesis of PMOS.	Multimomics study integrating lipidomics and proteomics analyses.	Alterations were identified in lipid metabolism and in proteins related to processes involved in the pathogenesis of PMOS.
Tabassum <i>et al.</i> (2021)	<i>Impact of polycystic ovary syndrome on quality of life of women in correlation to age, basal metabolic index, education and marriage</i>	To assess the impact of PMOS on quality of life and its relationship with sociodemographic characteristics and BMI.	Case-control study involving 100 women with PMOS and 200 controls, using the SF-36 questionnaire.	Women with PMOS experienced a significant reduction in quality of life, influenced by factors such as BMI, menstrual irregularity, and sociodemographic characteristics.
Wang <i>et al.</i> (2021)	<i>NAD⁺ deficiency and mitochondrial dysfunction in granulosa cells of women with polycystic ovary syndrome</i>	To investigate NAD ⁺ deficiency and mitochondrial dysfunction in granulosa cells.	Experimental and translational study involving granulosa cells from women with and without PMOS and assessing NAD ⁺ metabolism and mitochondrial function.	NAD ⁺ deficiency and mitochondrial dysfunction were identified in the granulosa cells of women with PMOS.
Yu <i>et al.</i> (2023)	<i>Incidence, prevalence, and trends in polycystic ovary syndrome diagnosis: a United States population-based study from 2006 to 2019</i>	To assess the incidence, prevalence, and temporal trends in PMOS diagnoses in the United States.	Retrospective population-based study using data from women aged 16 to 40 years between 2006 and 2019.	Variations in diagnosis rates were observed over the period according to age, race/ethnicity, and characteristics of care.
Yun <i>et al.</i> (2024)	<i>The microbial metabolite agmatine acts as an FXR agonist to promote polycystic ovary syndrome in female mice</i>	To investigate the role of agmatine and the FXR receptor in the pathophysiology of PMOS.	Experimental study involving female mice and analyses of the microbiota, agmatine, FXR signaling, and disease characteristics.	Agmatine acted as an FXR agonist and promoted alterations resembling those observed in PMOS, linking the microbiota, metabolism, and ovarian alterations.
Zhang <i>et al.</i> (2023)	<i>Relationship between body composition, insulin resistance, and hormonal profiles in women with polycystic ovary syndrome</i>	To assess the relationship among body composition, insulin resistance, and hormonal profiles in women with PMOS.	Comparative observational study assessing body composition, insulin resistance, and hormonal parameters.	Associations were observed among body composition, insulin resistance, and hormonal alterations in PMOS.

Zhao <i>et al.</i> (2021)	<i>Multiomics analysis reveals molecular abnormalities in granulosa cells of women with polycystic ovary syndrome</i>	To identify molecular alterations in the granulosa cells of women with PMOS.	Multiomics study integrating methylome, transcriptome, and metabolic analyses.	Molecular alterations associated with metabolism, steroidogenesis, and the regulation of gene expression were identified in granulosa cells.
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Source: Prepared by the authors (2026).

METABOLIC, HORMONAL, AND POLYENDOCRINE INTERRELATIONSHIPS

Polyendocrine Metabolic Ovarian Syndrome (PMOS) has characteristics that extend beyond exclusively ovarian and reproductive alterations, involving a complex interaction among metabolism, hormonal signaling, ovarian function, and cellular mechanisms. Farhadi-Azar et al. (2022), in investigating the prevalence, different phenotypes, and cardiometabolic characteristics of PMOS, demonstrated that its clinical presentation is heterogeneous and may involve different combinations of metabolic and reproductive alterations. Pratama et al. (2024) showed that women with a lean phenotype may also exhibit significant alterations in hormonal regulation, while Zhang et al. (2023) demonstrated relationships among body composition, insulin resistance, and hormonal profiles. In parallel, Liao et al. (2022) identified effects of androgen excess on granulosa cell metabolism and function. When analyzed together, these studies make it possible to characterize PMOS as a condition in which metabolic, hormonal, and reproductive components are functionally interconnected, warranting an understanding that extends beyond an exclusively ovary-centered interpretation.

Phenotypic heterogeneity is one of the first elements that must be considered to understand this relationship. Farhadi-Azar et al. (2022) demonstrated that PMOS may manifest through different phenotypes accompanied by distinct cardiometabolic characteristics. This differentiation is relevant because it shows that the condition does not have a single clinical expression. Women with greater adiposity may have more evident metabolic alterations, whereas women with a lean phenotype may predominantly exhibit hormonal and reproductive alterations. This does not, however, indicate the absence of metabolic alterations or mechanisms associated with PMOS. This issue was particularly

demonstrated by Pratama et al. (2024), who investigated the elevated ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) in women with a lean phenotype. LH and FSH are gonadotropins produced by the pituitary gland and are responsible for essential functions in regulating ovarian activity, including follicular development and ovulation. An elevated ratio between these two gonadotropins may reflect changes in communication within the hypothalamic-pituitary-ovarian axis, impairing the proper regulation of reproductive function.

The relationship among body composition, metabolism, and the hormonal system is further explored by Zhang et al. (2023), who identified an association among body composition, insulin resistance, and hormonal profiles in women with the syndrome. Insulin resistance is characterized by a reduced ability of tissues to respond adequately to the action of insulin, potentially leading to compensatory changes in the secretion of this hormone. This process is relevant to PMOS because altered insulin signaling may interfere with ovarian function and sex hormone production. At the same time, a hyperandrogenic environment may promote metabolic alterations, establishing a bidirectional relationship between metabolism and the endocrine system.

In this context, hyperandrogenism, characterized by excessive levels of androgens such as testosterone, constitutes an important link between hormonal and ovarian alterations. Liao et al. (2022) demonstrated that this condition is associated with metabolic alterations that may impair granulosa cell function and follicular development. These cells play an essential role in supporting the oocyte, producing hormones, and enabling the communication required for follicular maturation. Thus, androgen imbalance may alter the ovarian microenvironment and impair follicular maturation.

The metabolic repercussions on ovarian cells were also demonstrated by Wang et al. (2021), who identified nicotinamide adenine dinucleotide (NAD⁺) deficiency and mitochondrial dysfunction in the granulosa cells of women with the syndrome. NAD⁺ is an essential cofactor in reactions related to energy production and the maintenance of cellular homeostasis. Mitochondria are responsible for much of the energy production required for cellular function. Therefore, reduced NAD⁺ availability associated with

mitochondrial dysfunction may impair the energy capacity of granulosa cells and compromise the environment required for follicular development.

Zhao et al. (2021) reinforced this interpretation by identifying molecular alterations in granulosa cells through multiomics analysis. Multiomics analysis allows different levels of cellular activity to be investigated simultaneously, making it possible to identify alterations related to genes, proteins, and metabolites. The presence of alterations across multiple dimensions demonstrates that the ovarian dysfunction associated with PMOS results from a network of molecular changes rather than from a single isolated mechanism.

Qian et al. (2024) also contributed to this understanding by integrating lipid metabolomics and proteomics analyses. Metabolomics makes it possible to investigate changes in the set of metabolites present in the body, while proteomics assesses protein-related alterations. The identification of simultaneous changes in these pathways demonstrates a profound interaction between metabolism and ovarian function. Thus, molecular findings complement hormonal and metabolic evidence and help explain how systemic alterations may directly affect the cells involved in reproduction.

These results indicate that PMOS is not structured as a linear sequence of alterations but as a network of interdependent mechanisms. Hormonal dysregulation may promote metabolic alterations; insulin resistance may interfere with ovarian function; hyperandrogenism may modify follicular development; and alterations in energy metabolism may impair granulosa cells. These changes may, in turn, intensify reproductive dysfunction, establishing a feedback loop among metabolism, the endocrine system, and the ovary.

INTEGRATION AMONG THE MICROBIOTA, METABOLISM, AND OVARIAN FUNCTION

The characterization of PMOS as a metabolic and polyendocrine condition is also supported by studies investigating the involvement of the gut microbiota. Han et al. (2021) demonstrated that androgen excess can induce changes in the gut microbiota and interfere with glucose and lipid metabolism, while

Liang et al. (2021) identified microbial alterations associated with potential changes in the gut-brain axis. Yun et al. (2024) demonstrated in an experimental model that agmatine, a metabolite produced by microbial activity, can act on the farnesoid X receptor (FXR), also known as nuclear receptor NR1H4. Li et al. (2021b), in turn, observed an association among microbiota modulation, reduced intestinal oxidative stress, and improved ovarian dysfunction. These findings broaden the understanding of PMOS by demonstrating that the gut, metabolism, endocrine system, and ovary participate in an interconnected physiological network.

Han et al. (2021) demonstrated that androgen excess can modify the composition of the gut microbiota, with repercussions for glucose and lipid metabolism. This finding is important because it shows that a hormonal alteration characteristic of PMOS may affect a system located outside the reproductive tract. Changes in the microbiota may, in turn, alter metabolic processes and the availability of certain metabolites, creating conditions that maintain or intensify the systemic imbalance.

This relationship may also operate in the opposite direction. Alterations in the microbiota can modify the production and transformation of metabolites capable of acting on different organs. The gut is therefore no longer understood merely as a site affected by metabolic alterations but is instead regarded as a potential participant in the pathophysiology of PMOS. This perspective is important for understanding the polyendocrine nature of the condition, since different organs and systems may contribute to its maintenance.

Liang et al. (2021) added the potential involvement of the gut-brain axis to the discussion. This axis represents bidirectional communication among the gut, microbiota, microbial metabolites, and central nervous system. Because the central nervous system is involved in hormonal, metabolic, and reproductive regulation, alterations in this communication may affect mechanisms involved in PMOS. Accordingly, the changes observed in the microbiota may have implications that extend beyond intestinal metabolism and affect neuroendocrine mechanisms.

The involvement of microbial metabolites is even more evident in the study by Yun et al. (2024), who identified agmatine as a metabolite capable of acting as an agonist of the farnesoid X receptor (FXR), also known as nuclear receptor NR1H4. FXR is a nuclear receptor involved primarily in regulating bile acid homeostasis and is also implicated in glucose and lipid metabolism. The activation of this receptor demonstrates that molecules associated with microbial activity can directly interfere with metabolic signaling pathways.

In the experimental study by Yun et al. (2024), the action of agmatine on FXR was associated with the development of PMOS characteristics. This result is relevant because it provides a potential molecular explanation for the relationship between the microbiota and metabolic and reproductive alterations. However, because the study was conducted using an animal model, the finding does not establish that the same mechanism occurs identically in women. Nevertheless, it demonstrates that microbial metabolites may act as mediators between the intestinal environment and metabolic pathways associated with the syndrome.

Li et al. (2021b) added another mechanism by demonstrating in an experimental model that reduced intestinal oxidative stress and modulation of the microbiota were associated with improvements in ovarian dysfunction and glucose tolerance. Oxidative stress is an imbalance between the production of reactive species and the body's antioxidant capacity. This imbalance may cause cellular alterations and impair various physiological functions. The association identified in the study suggests that changes in the intestinal environment may simultaneously affect metabolism and ovarian function.

Taken together, these findings demonstrate that PMOS may involve continuous communication among the microbiota, metabolism, endocrine system, and ovary. Androgen excess may alter the microbiota; microbial changes may modify metabolites capable of acting on receptors such as FXR; and the resulting alterations may affect metabolism and ovarian function. This network of interactions helps explain why the condition has systemic manifestations and reinforces its characterization as metabolic and polyendocrine.

REPERCUSSIONS ON FERTILITY, QUALITY OF LIFE, AND THERAPEUTIC POSSIBILITIES

The interaction among hormonal, metabolic, cellular, and intestinal alterations has direct repercussions on fertility and the quality of life of women with PMOS. Liao et al. (2022) demonstrated that metabolic alterations associated with androgen excess may impair granulosa cells and follicular development, while Wang et al. (2021) identified NAD⁺ deficiency and mitochondrial dysfunction in these cells. Zhao et al. (2021) also identified molecular alterations in granulosa cells, and Chen et al. (2022) demonstrated the importance of communication between the oocyte and granulosa cells. In parallel, Tabassum et al. (2021) documented the condition's repercussions on quality of life, while Yu et al. (2023) demonstrated the population-level relevance of its diagnoses. These findings indicate that the repercussions of PMOS extend beyond ovulation and involve cellular, metabolic, hormonal, reproductive, and psychosocial mechanisms.

In this context, infertility should not be interpreted as the consequence of a single ovarian disorder. Ovulatory alterations may be related to gonadotropin dysregulation, insulin resistance, hyperandrogenism, and metabolic changes that interfere with ovarian function. Liao et al. (2022) demonstrated that androgen excess can impair granulosa cell function and follicular development, establishing a connection between hormonal imbalance and reproductive capacity.

Wang et al. (2021) added a metabolic dimension to this relationship by identifying NAD⁺ deficiency and mitochondrial dysfunction in granulosa cells. Because these cells depend on adequate energy metabolism to perform their functions, mitochondrial alterations may compromise the support required for follicular development. Thus, infertility associated with PMOS may result from the convergence of hormonal and metabolic alterations that impair different stages of the reproductive process.

In investigating transzonal projections, which are structures involved in communication between the oocyte and granulosa cells, Chen et al. (2022) observed favorable effects of resveratrol on this interaction. This communication is essential to proper oocyte maturation and maintenance of the follicular

environment, demonstrating that specific cellular mechanisms may represent potential targets for future interventions.

The molecular alterations identified by Zhao et al. (2021) and the metabolic changes observed by Qian et al. (2024) reinforce the understanding that ovarian function depends on a complex molecular organization. Alterations in genes, proteins, lipids, and metabolites may modify the environment required for follicular maturation. Infertility should therefore not be reduced to the absence of ovulation, as the quality and functional competence of the ovarian environment may also be affected.

In addition to its reproductive repercussions, PMOS has a significant impact on quality of life. Tabassum et al. (2021) demonstrated an association between the condition and impairments related to health and well-being. Menstrual irregularity, bodily changes, and fertility-related difficulties may have emotional and social consequences, affecting self-esteem, interpersonal relationships, and perceptions of quality of life. Women's holistic health therefore requires these aspects to be considered alongside metabolic and hormonal markers.

The therapeutic possibilities investigated also reinforce the relationship between metabolism and reproduction. Cincione et al. (2021) assessed the effects of a ketogenic diet in women with overweight or obesity and observed changes in parameters associated with the condition. Magagnini et al. (2022) discussed the potential repercussions of this strategy on ovarian function. These findings suggest that modifying the metabolic environment may affect reproductive manifestations. However, the findings must be interpreted in light of the participants' profiles, and the effects observed cannot automatically be extrapolated to women with a lean phenotype.

Li et al. (2021a) demonstrated that eight-hour time-restricted feeding was associated with improved endocrine and metabolic parameters in women with anovulatory PMOS. This result reinforces the relationship between metabolism and reproductive function, indicating that changes in eating patterns may affect different components of PMOS. However, the use of nutritional interventions must take individual metabolic, hormonal, and reproductive characteristics into account.

In the field of molecular therapies, Chen et al. (2022) demonstrated the effects of resveratrol on communication between the oocyte and granulosa cells, while Cao et al. (2022) investigated microRNAs derived from exosomes secreted by adipose tissue mesenchymal stem cells. MicroRNAs are small ribonucleic acid molecules involved in regulating gene expression, while exosomes are vesicles released by cells that can transport biologically active molecules. These studies demonstrate that investigating cellular and molecular mechanisms may open possibilities for interventions targeting specific components of PMOS.

The diversity of the strategies investigated reflects the pathophysiological complexity of the condition itself. Nutritional interventions may act on metabolism; microbiota-targeted strategies may interfere with intestinal and metabolic mechanisms; bioactive compounds may modify cellular processes; and molecular approaches may act on pathways associated with ovarian function. This diversity reinforces the fact that no single dimension can explain or treat all manifestations of PMOS.

CONCLUSION

The complex interfaces among hormonal dysfunction, metabolic alterations, gut microbiota dynamics, and reproductive health in Polyendocrine Metabolic Ovarian Syndrome (PMOS) demonstrate that this condition extends beyond the reproductive tract and is characterized as a systemic, multifactorial syndrome. In this context, hyperandrogenism, insulin resistance, oxidative stress, and gut dysbiosis interact dynamically, establishing a continuous feedback loop that contributes to the persistence and progression of metabolic, hormonal, and reproductive alterations.

The studies demonstrate that the syndrome's phenotypic heterogeneity requires moving beyond a perspective centered exclusively on ovarian morphology. Relevant molecular alterations have been identified in granulosa cells within the follicular microenvironment, including NAD⁺ deficiency, mitochondrial dysfunction, and impairment of the transzonal projections responsible for communication with the oocyte. These alterations may contribute to reduced oocyte quality and impaired follicular

development, including in women with a lean phenotype. Furthermore, incorporating the microbiota-gut-brain axis broadens the understanding of the syndrome by showing that microbial metabolites, such as agmatine, and changes in intestinal permeability may participate actively in the dysregulation of glucolipid metabolism and the maintenance of a systemic inflammatory state.

The methodological diversity of the included studies should be emphasized, as they encompass different study designs and investigative models. This aspect requires caution when interpreting and generalizing certain molecular findings to the clinical context. Longitudinal studies and longer-duration clinical trials are recommended, as are multiomics and translational investigations that may contribute to assessing integrated interventions involving nutritional, pharmacological, and mental health strategies for managing and preventing the cardiometabolic and reproductive complications associated with PMOS.

In summary, the management of PMOS requires a transdisciplinary and holistic clinical approach capable of integrating lifestyle interventions, nutritional strategies such as time-restricted feeding and dietary modulation, microbiome-targeted therapies, and new bioactive target molecules. Care for women with PMOS should aim not only to restore ovulation or achieve isolated metabolic control, but also to alleviate psychosocial impacts and promote long-term quality of life.

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