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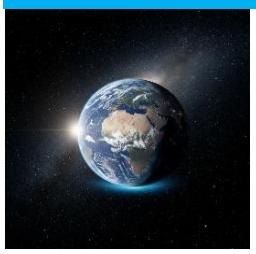

Journal of Education, Health and Sport. eISSN 2391-8306.

Journal Home Page
https://apcz.umk.pl/JEHS/index

LECH, Jakub, MARCINKOWSKA, Anna, NOWOSIELSKA, Julia, STOBIŃSKI, Karol, PŁUSA, Aleksandra, PLUTA, Natalia, BARCZUK, Patryk, ZAŁUSKA, Urszula, KOPYT, Weronika and LATALSKA, Katarzyna. Gut - Brain - Ovary Axis in Polycystic Ovary Syndrome: Microbiota, Metabolic Inflammation, and Reproductive Dysfunction. Journal of Education, Health and Sport. 2026;89:69973. eISSN 2391-8306. https://doi.org/10.12775/JEHS.2026.89.69973

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.03.2026. Revised: 06.04.2026. Accepted: 06.04.2026. Published: 10.04.2026.

Gut - Brain - Ovary Axis in Polycystic Ovary Syndrome: Microbiota, Metabolic Inflammation, and Reproductive Dysfunction

Authors:

1. **Jakub Lech**[1]

jakub.lech2016@gmail.com

https://orcid.org/0009-0004-0883-5819

2. **Anna Marcinkowska**[1]

anna.marcinkowska2406@gmail.com

https://orcid.org/0009-0007-7363-6914

3. Julia Nowosielska[1]

juliairenanowosielska@gmail.com

https://orcid.org/0009-0005-5184-0258

4. Karol Stobiński[1]

karol17gm@gmail.com

https://orcid.org/0009-0005-9075-0335

5. Aleksandra Płusa[1]

plusa.aleksandra22@gmail.com

https://orcid.org/0009-0009-4307-8899

6. Natalia Pluta[1]

3bnataliapluta@gmail.com

https://orcid.org/0009-0003-2112-3069

7. Patryk Barczuk[1]

Patryk.barczuk11235@gmail.com

https://orcid.org/0009-0004-2271-8782

8. Urszula Załuska[1]

Urszaluska@gmail.com

https://orcid.org/0009-0008-4666-8790

9. Weronika Kopyt[1]

weronikakopyt1@gmail.com

https://orcid.org/0009-0002-2295-4967

10. Katarzyna Latalska[2]

latalska.k@gmail.com

https://orcid.org/0009-0009-8102-8948

Place of affiliation:

[1] Masovian Specialist Hospital, Juliana Aleksandrowicza 5, 26-617 Radom, Poland

[2] University Clinical Hospital No. 4, Dr. K. Jaczewski Street 8, 20-090 Lublin, Poland

Corresponding author: Jakub Lech[1] Masovian Specialist Hospital, Juliana Aleksandrowicza 5, 26-617 Radom, Poland Jakub.lech2016@gmail.com

https://orcid.org/0009-0004-0883-5819

Abstract

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder characterized by reproductive, metabolic, and inflammatory disturbances. Increasing evidence suggests that gut microbiota plays a significant role in the regulation of metabolic and neuroendocrine pathways involved in PCOS.

Aim

The aim of this review was to summarize current knowledge on the gut-brain-ovary axis in PCOS, with particular focus on the contribution of gut microbiota dysbiosis to metabolic inflammation and reproductive dysfunction.

Material and methods

A narrative review of the literature was conducted using PubMed/MEDLINE, Scopus, and Web of Science databases. Peer-reviewed articles published in English up to March 2024 were analyzed. Studies addressing associations, underlying mechanisms, and therapeutic interventions linking gut microbiota with metabolic, inflammatory, neuroendocrine, and reproductive features of PCOS were included.

Results

Available evidence indicates that women with PCOS exhibit significant alterations in gut microbiota composition, including reduced microbial diversity, decreased abundance of short-chain fatty acid-producing bacteria, and increased prevalence of pro-inflammatory taxa. These changes are associated with insulin resistance, impaired intestinal barrier function, metabolic endotoxemia, chronic low-grade inflammation, hyperandrogenism, and disturbances in hypothalamic-pituitary-ovarian signaling.

Conclusions

Gut microbiota dysbiosis appears to play an important integrative role in the pathophysiology of PCOS by linking metabolic inflammation with neuroendocrine and ovarian dysfunction. The gut-brain-ovary axis represents a promising conceptual framework and therapeutic target; however, further well-designed longitudinal and mechanistic studies are required.

Keywords:

polycystic ovary syndrome, gut microbiota, gut-brain-ovary axis, insulin resistance, chronic inflammation, probiotics

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders affecting women of reproductive age, with a prevalence estimated at 8-13%, depending on diagnostic criteria and the population studied [1]. It is characterized by a heterogeneous clinical presentation that includes hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, frequently accompanied by insulin resistance, obesity, and an increased risk of cardiometabolic disease [2]. Despite extensive research and the availability of international evidence-based guidelines, the pathophysiology of PCOS remains incompletely understood, limiting the development of targeted and causative therapies [1,3].

Traditionally, PCOS has been viewed primarily as a disorder of ovarian steroidogenesis and hypothalamic-pituitary regulation [4]. However, accumulating evidence indicates that PCOS is a systemic condition involving complex interactions among metabolic, inflammatory, and neuroendocrine pathways [5]. Chronic low-grade inflammation and insulin resistance are now recognized as central features of the syndrome and are thought to play a pivotal role in both reproductive and metabolic dysfunction [4,6]. These processes not only exacerbate hyperandrogenism and follicular arrest but also contribute to the long-term cardiovascular and metabolic complications observed in women with PCOS [2,7].

In recent years, the gut microbiota has emerged as a key regulator of host metabolism, immune homeostasis, and endocrine function [7]. Advances in metagenomic and metabolomic techniques have revealed consistent alterations in gut microbial composition and diversity in women with PCOS compared with healthy controls [3,8,9]. Dysbiosis in PCOS has been associated with increased intestinal permeability, altered bile acid metabolism, endotoxemia, and activation of inflammatory signaling pathways [10,11]. Importantly, several studies have demonstrated correlations between gut microbiota profiles and core PCOS features, including hyperandrogenism, insulin resistance, and body mass index, suggesting that microbial alterations may not merely be a consequence of the syndrome but may actively contribute to its pathogenesis [6,12].

Beyond metabolic effects, the gut microbiota is increasingly recognized as an important modulator of neuroendocrine communication through the gut-brain axis [13]. Microbial metabolites, such as short-chain fatty acids, bile acids, and tryptophan derivatives, can influence

hypothalamic signaling, appetite regulation, stress responses, and gonadotropin secretion [13,14]. In parallel, ovarian function appears sensitive to inflammatory and metabolic signals originating from both the gut and the central nervous system [14]. These observations have led to the concept of a gut-brain-ovary axis, a bidirectional network through which intestinal microbiota may affect reproductive endocrinology and ovarian physiology [12,13].

Experimental evidence has strengthened the biological plausibility of this axis in PCOS. Animal models have demonstrated that transplantation of gut microbiota from women with PCOS can induce metabolic disturbances, hyperandrogenism, and ovarian dysfunction in germ-free mice [15]. Moreover, genetic and Mendelian randomization studies suggest potential causal relationships between specific microbial taxa and PCOS risk [16,17]. Therapeutic interventions that modulate the gut microbiota, including lifestyle modification, probiotics, prebiotics, and metformin, have shown beneficial effects on metabolic and hormonal parameters, further supporting a functional link between intestinal microbes and PCOS manifestations [18-20].

Given the growing body of evidence, an integrated framework linking gut microbiota dysbiosis, metabolic inflammation, neuroendocrine regulation, and ovarian dysfunction is increasingly warranted [21]. This review aims to synthesize current knowledge on the gut-brain-ovary axis in PCOS, focusing on the role of the gut microbiota in driving metabolic inflammation and reproductive abnormalities [8,22]. By elucidating these interconnected pathways, emerging mechanistic insights are highlighted, and potential microbiota-targeted strategies that may complement existing approaches to PCOS management are identified [5].

2. Aim of the study

The aim of this review was to summarize current evidence on the role of the gut-brain-ovary axis in polycystic ovary syndrome, with particular emphasis on gut microbiota dysbiosis, metabolic inflammation, and reproductive dysfunction.

3. Material and methods

This work was conducted as a narrative, integrative review aimed at synthesizing current evidence on the role of the gut-brain-ovary axis in the pathophysiology of polycystic ovary syndrome (PCOS), with particular emphasis on gut microbiota dysbiosis, metabolic inflammation, and reproductive dysfunction. Given the heterogeneity of available study designs

and the emerging nature of this research field, a narrative approach was selected to allow comprehensive integration of clinical, experimental, and mechanistic data.

A structured literature search was performed to identify relevant peer-reviewed publications. Electronic databases including PubMed/MEDLINE, Scopus, and Web of Science were searched for articles published up to March 2024. The search strategy combined controlled vocabulary and free-text terms related to PCOS and gut microbiota, including but not limited to: “polycystic ovary syndrome,” “PCOS,” “gut microbiota,” “gut dysbiosis,” “intestinal permeability,” “metabolic inflammation,” “insulin resistance,” “hyperandrogenism,” “gut-brain axis,” and “reproductive dysfunction.” Boolean operators (“AND,” “OR”) were used to refine the search. Reference lists of selected articles and relevant review papers were also manually screened to identify additional studies not captured in the initial search.

Original research articles, systematic reviews, and meta-analyses published in English were considered eligible if they investigated associations or mechanisms linking gut microbiota with metabolic, inflammatory, neuroendocrine, or reproductive features of PCOS. Both human and animal studies were included to provide mechanistic insight, particularly where experimental data supported causality. Studies focusing exclusively on non-PCOS populations, non-gut microbial ecosystems, or unrelated endocrine disorders were excluded. Conference abstracts, editorials, and non-peer-reviewed sources were not considered.

Titles and abstracts identified through the database search were screened for relevance. Full texts were subsequently reviewed when abstracts met inclusion criteria or when relevance was unclear. Data were extracted qualitatively, focusing on study design, population characteristics, diagnostic criteria for PCOS, methods used to assess gut microbiota and metabolic or hormonal parameters, and key findings related to inflammation, insulin resistance, and reproductive outcomes. Given the narrative nature of this review, no formal quantitative synthesis or meta-analysis was performed.

The included studies were evaluated with attention to methodological quality, consistency of findings, and biological plausibility. Particular emphasis was placed on studies using metagenomic, metabolomic, and functional analyses, as well as experimental models such as fecal microbiota transplantation and Mendelian randomization approaches. Findings were synthesized thematically to construct an integrated framework describing interactions between gut microbiota, metabolic inflammation, neuroendocrine regulation, and ovarian function within the gut-brain-ovary axis.

As this study was based exclusively on previously published data, no ethical approval or informed consent was required. All included studies were assumed to have been conducted in accordance with applicable ethical standards.

This methodological approach was designed to provide a comprehensive and balanced overview of current evidence while identifying knowledge gaps and future research directions relevant to microbiota-targeted strategies in PCOS.

4. Results

Alterations in Gut Microbiota Composition and Diversity in PCOS

Across multiple cross-sectional and metagenomic studies, women with polycystic ovary syndrome (PCOS) consistently demonstrated significant alterations in gut microbiota composition compared with healthy controls [3,8,9,21]. Alpha diversity indices, including Shannon, Chao1, and Faith's phylogenetic diversity, were reduced in most PCOS cohorts, indicating decreased microbial richness and evenness [6,22]. Quantitative analyses showed significantly lower observed sequence variants and Faith's PD in PCOS compared with controls ($P=0.04$ and $P=0.02$, respectively), with more pronounced reductions in insulin-resistant and hyperandrogenic PCOS phenotypes [6].

Beta diversity analyses revealed distinct clustering of PCOS-associated microbial communities, suggesting disease-specific microbial signatures independent of geographic and dietary background [10,21]. Machine learning-based classification models using gut microbiota features achieved moderate discrimination between PCOS and healthy women, with a classification accuracy of approximately 65% for PCOS and 50% for controls, highlighting partial but reproducible microbial separation between groups [6].

At the taxonomic level, PCOS was associated with a relative depletion of beneficial commensal bacteria, particularly short-chain fatty acid (SCFA)-producing taxa such as *Faecalibacterium prausnitzii*, *Roseburia* spp., *Ruminococcus bromii*, and *Bifidobacterium* spp. [8,22]. In contrast, enrichment of pro-inflammatory and lipopolysaccharide-producing taxa was repeatedly observed, including *Escherichia/Shigella*, *Prevotella*, *Desulfovibrio*, *Parabacteroides merdae*, and *Bacteroides fragilis* [3,9-11]. Additional discriminatory taxa identified in PCOS included *Bacteroides coprophilus*, *Porphyromonas* spp., and *Blautia* spp., whereas *Odoribacter* spp. and *Anaerococcus* spp. were more abundant in healthy controls [6]. Several studies also reported an increased Firmicutes-to-Bacteroidetes ratio, particularly in overweight and insulin-resistant PCOS subgroups, aligning PCOS-related dysbiosis with patterns observed in obesity and metabolic syndrome [7,21].

Association of Microbiota Dysbiosis with Metabolic Dysfunction

Gut microbiota alterations in PCOS were closely associated with metabolic abnormalities, particularly insulin resistance [5,22]. Reduced microbial diversity and depletion of SCFA-producing taxa showed negative correlations with insulin sensitivity markers, including HOMA-IR, fasting insulin, and fasting glucose levels [6,8]. Conversely, increased abundance of gram-negative, endotoxin-producing bacteria correlated positively with systemic insulin resistance, dyslipidemia, and central adiposity [7,11].

Functional metagenomic analyses demonstrated disrupted microbial pathways related to bile acid metabolism, branched-chain amino acid biosynthesis, and carbohydrate fermentation in PCOS [8,12]. Women with PCOS also exhibited altered bile acid profiles and reduced circulating fibroblast growth factor-19 (FGF-19), indicating impaired gut-liver signaling [23]. These metabolic alterations were accompanied by increased intestinal permeability, reflected by elevated circulating zonulin and endotoxin concentrations, suggesting compromised gut barrier integrity [10,24].

Gut-Derived Inflammation and Immune Activation

Markers of low-grade chronic inflammation were consistently elevated in women with PCOS and were strongly associated with gut microbiota dysbiosis [4,11]. Increased circulating concentrations of C-reactive protein, tumor necrosis factor-α, interleukin-6, and interleukin-18 correlated with reduced microbial diversity and enrichment of pro-inflammatory taxa [14]. Studies assessing intestinal permeability reported higher serum levels of lipopolysaccharide (LPS) and LPS-binding protein in PCOS compared with healthy women, supporting the presence of metabolic endotoxemia [10,24].

This gut-derived inflammatory state was closely linked to impaired insulin signaling. Activation of inflammatory pathways, including NF-κB signaling, was observed in association with endotoxin exposure and contributed to peripheral insulin resistance [4,14]. Collectively, these findings indicate that gut microbiota-driven inflammation represents a key mechanistic link between dysbiosis and metabolic dysfunction in PCOS.

Relationship Between Gut Microbiota and Reproductive Hormonal Disturbances

Several studies identified significant associations between gut microbial composition and reproductive hormone profiles in PCOS [6,9]. Reduced alpha diversity and specific taxonomic shifts correlated positively with circulating androgen levels, including total testosterone and

free androgen index [6]. Hyperandrogenic PCOS phenotypes exhibited stronger enrichment of taxa associated with inflammation and metabolic dysfunction, suggesting a bidirectional interaction between androgen excess and gut microbiota composition [6,25].

Alterations in microbial metabolites, particularly SCFAs and bile acids, were also linked to dysregulation of the hypothalamic-pituitary-ovarian axis [13,23]. These changes were associated with altered gonadotropin secretion patterns, including elevated luteinizing hormone concentrations and increased LH/FSH ratios, which are characteristic of PCOS-related ovulatory dysfunction [1,14].

Evidence from Causal and Interventional Studies

Emerging evidence from Mendelian randomization analyses supports a potential causal role of specific gut microbial taxa in PCOS susceptibility [16,17]. Increased genetically predicted abundance of taxa such as Bacilli (OR 1.76), Burkholderiales (OR 2.37), and Lachnospiraceae (OR 1.86) was associated with a higher risk of PCOS, whereas taxa including *Bilophila* (OR 0.42), *Blautia* (OR 0.16), *Holdemania* (OR 0.53), and *Candidatus Soleaferrea* (OR 0.65) were associated with reduced PCOS risk [16]. Complementary analyses identified additional risk-associated genera, including *Streptococcus* (OR 1.55) and *Actinomyces* (OR 1.37), as well as potentially protective taxa such as *Dorea* and *Ruminococcaceae UCG-011* [17].

Experimental studies further supported these findings; fecal microbiota transplantation from women with PCOS into germ-free mice induced insulin resistance, systemic inflammation, disrupted estrous cyclicity, and ovarian morphological changes consistent with PCOS phenotypes [15]. Interventional studies targeting the gut microbiota demonstrated partial improvement of metabolic and inflammatory parameters. Probiotic supplementation was associated with modest improvements in insulin sensitivity, androgen levels, and inflammatory markers, alongside favorable shifts in gut microbial composition [18,19]. Metformin treatment consistently increased microbial diversity, enriched SCFA-producing taxa, and reduced endotoxin-related inflammation, suggesting that part of its therapeutic effect may be mediated through modulation of the gut microbiota [20].

Integrated Gut-Brain-Ovary Axis Disruption

Collectively, the results indicate that PCOS is characterized by a reproducible pattern of gut microbiota dysbiosis that is closely linked to metabolic inflammation and reproductive dysfunction [12,25]. Altered microbial composition, impaired gut barrier function, and chronic low-grade inflammation appear to converge on neuroendocrine and ovarian pathways,

disrupting insulin signaling, androgen synthesis, and ovulatory function [5,14]. These findings support the existence of a dysregulated gut-brain-ovary axis in PCOS and highlight the gut microbiota as a central component in the pathophysiology of the syndrome [25].

5. Discussion

The findings synthesized in this review support the concept that polycystic ovary syndrome (PCOS) is not solely a reproductive disorder but a complex systemic condition in which gut microbiota dysbiosis plays an integral role in metabolic, inflammatory, and neuroendocrine dysfunction [5,12]. Accumulating evidence suggests that alterations in gut microbial composition and function contribute to the disruption of the gut-brain-ovary axis, thereby linking metabolic inflammation with reproductive abnormalities characteristic of PCOS [5,12,25].

A consistent observation across studies is the reduction in gut microbial diversity in women with PCOS, particularly in those with insulin resistance and hyperandrogenism [6,21,22]. Reduced diversity is widely considered a marker of impaired ecosystem resilience and has been linked to metabolic disorders such as obesity and type 2 diabetes [7]. In PCOS, the depletion of beneficial short-chain fatty acid (SCFA)-producing bacteria appears especially relevant, as SCFAs regulate intestinal barrier integrity, glucose metabolism, and immune tolerance [8,13]. Their reduction may therefore predispose individuals with PCOS to increased gut permeability and chronic low-grade inflammation, both of which are well-recognized contributors to insulin resistance [4,10].

The present body of evidence supports a mechanistic link between gut dysbiosis and metabolic inflammation in PCOS. Enrichment of gram-negative, lipopolysaccharide-producing bacteria has been repeatedly associated with elevated circulating endotoxin levels and inflammatory cytokines [10,11,24]. This metabolic endotoxemia may activate inflammatory signaling pathways, such as NF-κB, impair insulin signaling, and exacerbate hyperinsulinemia [4,14]. Hyperinsulinemia, in turn, stimulates ovarian androgen production and suppresses hepatic sex hormone-binding globulin synthesis, reinforcing hyperandrogenism [2,6]. This feed-forward loop highlights how gut-derived inflammatory signals may act upstream of key endocrine disturbances in PCOS [5].

Importantly, the relationship between the gut microbiota and reproductive dysfunction extends beyond metabolic pathways. Several studies demonstrate correlations between specific microbial taxa and circulating androgen levels, as well as alterations in gonadotropin secretion patterns [6,9]. These findings suggest that microbial metabolites, bile acids, and inflammatory

mediators may influence hypothalamic and pituitary function, thereby modulating the hypothalamic-pituitary-ovarian axis [13,14]. Disrupted bile acid signaling and reduced fibroblast growth factor-19 levels observed in PCOS further support impaired gut-liver-brain communication, with potential downstream effects on appetite regulation, energy homeostasis, and reproductive hormone secretion [23].

Experimental evidence strengthens the argument for a causal role of the gut microbiota in PCOS pathophysiology. Fecal microbiota transplantation from women with PCOS into germ-free mice has been shown to induce insulin resistance, systemic inflammation, and ovarian dysfunction, recapitulating key features of the syndrome [15]. Moreover, recent Mendelian randomization studies suggest that genetically predicted variations in specific microbial taxa are associated with PCOS risk, providing support for a directional relationship rather than mere association [16,17]. While these approaches have inherent limitations, together they suggest that gut dysbiosis may actively contribute to disease development and progression [25].

From a clinical perspective, these insights have important therapeutic implications. Current international guidelines emphasize lifestyle modification and metabolic risk reduction as central components of PCOS management [1,2]. The gut microbiota may represent a modifiable target through which such interventions exert part of their benefit [12]. Probiotic supplementation trials have demonstrated modest improvements in insulin sensitivity, inflammatory markers, and androgen profiles, although results remain heterogeneous [18,19]. Differences in probiotic strains, dosages, treatment duration, and PCOS phenotypes likely contribute to variable outcomes and underscore the need for more standardized and mechanistically informed trials [25].

Metformin, a cornerstone of PCOS treatment, has also been shown to modulate gut microbiota composition, increasing microbial diversity and SCFA-producing bacteria while reducing pro-inflammatory taxa [20]. This raises the possibility that some of metformin's metabolic and endocrine benefits are mediated indirectly through the gut microbiome rather than solely through direct effects on hepatic glucose production and insulin sensitivity [5,12]. Emerging therapeutic strategies, including microbiota-derived metabolites and personalized microbiome interventions, represent promising but still experimental approaches that warrant further investigation [25].

Despite substantial progress, several gaps remain in the current literature. Most human studies are cross-sectional, limiting causal inference, and are often confounded by differences in diet, body mass index, ethnicity, and medication use [21,22]. Additionally, PCOS is a heterogeneous condition, and gut microbiota signatures may differ across phenotypes, ages, and metabolic

profiles [6]. Longitudinal studies integrating multi-omics approaches with detailed clinical phenotyping are needed to clarify temporal relationships and identify clinically relevant microbial targets [12,25].

In conclusion, the available evidence supports a central role for gut microbiota dysbiosis in linking metabolic inflammation with reproductive dysfunction in PCOS [5,25]. Disruption of the gut-brain-ovary axis provides a unifying framework that integrates metabolic, immune, and neuroendocrine abnormalities observed in this syndrome [13,14]. A deeper understanding of these interactions may enable the development of more precise, mechanism-based interventions aimed at improving both metabolic and reproductive outcomes in women with PCOS [1,12].

7. Conclusions

This review highlights the gut-brain-ovary axis as a compelling and integrative framework for understanding the complex pathophysiology of polycystic ovary syndrome. Accumulating evidence indicates that gut microbiota dysbiosis is closely intertwined with metabolic inflammation, insulin resistance, and neuroendocrine disturbances that collectively drive reproductive dysfunction in PCOS. Rather than representing an isolated ovarian disorder, PCOS emerges as a systemic condition in which intestinal microbial alterations may act as upstream modulators of endocrine and metabolic homeostasis.

Altered gut microbial composition, reduced diversity, impaired barrier function, and dysregulated microbial metabolites appear to converge on inflammatory and insulin signaling pathways, amplifying hyperandrogenism and ovulatory dysfunction. At the same time, interactions between the gut microbiota and central neuroendocrine regulation suggest that microbial signals may influence hypothalamic-pituitary activity, further reinforcing hormonal imbalance. Experimental and genetic evidence increasingly supports a contributory, and potentially causal, role of the gut microbiota in the development and persistence of PCOS features.

From a clinical perspective, these insights underscore the potential of microbiota-targeted strategies as adjunctive approaches in PCOS management. Lifestyle interventions, pharmacological treatments such as metformin, and emerging microbiome-based therapies may exert part of their beneficial effects through modulation of the gut ecosystem. However, the heterogeneity of PCOS and the complexity of host-microbe interactions necessitate cautious interpretation of current findings and highlight the need for personalized approaches.

Future research should prioritize longitudinal and interventional studies integrating multi-omics technologies with detailed phenotypic characterization to clarify causality, identify robust

microbial biomarkers, and define therapeutic targets within the gut-brain-ovary axis. A deeper mechanistic understanding of these interconnected pathways may ultimately facilitate the development of more precise, mechanism-based interventions aimed at improving both metabolic health and reproductive outcomes in women with PCOS.

DISCLOSURES:

Authors' contribution:

Conceptualization: Jakub Lech

Methodology: Aleksandra Płusa, Jakub Lech

Software: not applicable

Check: Anna Marcinkowska, Urszula Załuska

Formal analysis: Karol Stobiński

Investigation: Patryk Barczuk, Karol Stobiński

Resources: Julia Nowosielska

Data curation: Weronika Kopyt, Patryk Barczuk

Writing -rough preparation: Natalia Pluta

Writing -review and editing: Weronika Kopyt

Visualization: Jakub Lech, Aleksandra Płusa

Supervision: Urszula Załuska, Katarzyna Latalska

Project administration: Natalia Pluta, Jakub Lech

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This research received no external funding.

Institutional Review Board Statement: This study is a narrative review based exclusively on previously published data; therefore, ethical approval and informed consent were not required.

Informed Consent Statement: Not Applicable.

Data Availability Statement: Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conflict of Interest: The authors declare no conflict of interest.

During the preparation of this work, the author(s) used Google's Chat Generative Pre-trained Transformer (Gemini 3) to support the editing process, including grammar, spelling, punctuation, and stylistic refinement. All content generated with AI assistance was

carefully reviewed and revised by the author(s), who accept full responsibility for the accuracy, interpretation, and integrity of the final manuscript.

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