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Gut Microbiota as Environmental Modulators of Hormonal Balance in Women: A Systematic Review of Probiotic Interventions in PCOS

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الميكروبيوم المعوي كمنظم بيئي للتوازن الهرموني لدى النساء: مراجعة نقدية لتدخلات البروبيوتيك في متلازمة تكيس المبايض

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Abstract:
Gut microbiota is recognized emerging evidence as a putative environmental controller of hormonal balance in women, especially in polycystic ovary syndrome (PCOS). This is a review of the current clinical evidence, focusing on recent studies that have determined the effects of multi-strain probiotics on endocrine profiles and body mass index (BMI) in PCOS patients. Although promising with outcomes such as TSH, SHBG, and Free Androgen Index (FAI) changes, the primary limitations of short study duration, population size, and lack of microbiota profiling negate the interpretability. The article brings to light the need for mechanistic insights, stratified probiotic interventions, and large-scale research to validate the microbiome-hormone axis as a viable therapeutic target. Recent advances in microbiome science suggest that dysbiosis of the gut may be involved in many metabolic and hormonal dysregulations seen in PCOS. Probiotic supplementation, particularly with multi-strain formulations, has shown promise in reducing androgen levels, enhancing insulin sensitivity, and enhancing markers of endocrine function. In addition, heterogeneity of dosage, duration, and strains poses a major barrier to generalization. Second, the absence of routine gut microbiota profiling in the majority of clinical trials limits our understanding of strain-specific mechanisms and concomitant biological determinants. Because PCOS is a multi-factorial condition, future studies must adopt integrative approaches combining metagenomics, metabolomics, and endocrinology to tailor probiotic treatment. Overall, current evidence projects a robust but incomplete picture of therapeutic promise for gut microbiota modulation in the treatment of PCOS.

Keywords: PCOS, gut microbiota, probiotics, hormonal homeostasis, BMI, endocrine function, microbiome-hormone axis, dysbiosis.

الملخص:
تُسلّط الأبحاث الناشئة الضوء على ميكروبات الأمعاء كمُعدِّل بيئي مُحتمل للتوازن الهرموني لدى النساء متلازمة تكيس المبايض تُجري هذه هذه دراسةًالمرجعيه نقديةً للأدلة السريرية الحالية، مُركِّزة على الدراسات الحديثة التي تُقيّم تأثير البروبيوتيك متعدد السلالات على الملامح الهرمونية ومؤشر كتلة الجسم (BMI) لدى مريضات متلازمة تكيس المبايض. على الرغم من النتائج الواعدة، مثل تحسُّن مستويات هرمونTSH ، وهرمونSHBG ، ومؤشر الأندروجين الحر(FAI) ، إلا أن القيود الرئيسية، مثل قصر المدة، وصغر حجم العينة، ونقص توصيف ميكروبات الأمعاء، تُعيق إمكانية التفسير. تُؤكِّد هذه الورقة البحثية على الحاجة إلى وضوح آلية العلاج، ونهج مُخصَّصة للبروبيوتيك، ودراسات أوسع نطاقًا للتحقق من صحة محور الميكروبيوم-الهرمون كهدف علاجي فعّال. تشير التطورات الحديثة في علم الميكروبيوم إلى أن خلل التوازن البكتيري في الأمعاء قد يُسهم في الاضطرابات الأيضية والهرمونية المُلاحظة في متلازمة تكيس المبايض. وقد أظهرت مكملات البروبيوتيك، وخاصةً تلك المُصنّعة من سلالات متعددة، قدرتها على خفض مستويات الأندروجين، وتعديل حساسية الأنسولين، وتعزيز مؤشرات وظائف الغدد الصماء. ومع ذلك، لا يزال التباين في الجرعة والمدة واختيار السلالة يُشكّل عائقًا رئيسيًا أمام التعميم. علاوة على ذلك، فإن غياب التوصيف الروتيني لميكروبات الأمعاء في العديد من التجارب السريرية يُحدّ من فهمنا للتأثيرات الخاصة بكل سلالة والآليات البيولوجية الكامنة وراءها. ونظرًا لأن متلازمة تكيس المبايض حالة متعددة العوامل، يجب أن تتبنى الدراسات المستقبلية مناهج تكاملية تجمع بين علم الجينوم وعلم الأيض وعلم الغدد الصماء لتصميم علاج مُخصص للبروبيوتيك. بشكل عام، تُقدم الدراسات الحالية صورة مُقنعة، وإن كانت غير كاملة، عن الوعد العلاجي لتعديل ميكروبات الأمعاء في إدارة متلازمة تكيس المبايض.

الكلمات المفتاحية: متلازمة تكيس المبايض، ميكروبات الأمعاء، البروبيوتيك، التوازن الهرموني، مؤشر كتلة الجسم، صحة الغدد الصماء، محور الميكروبيوم-الهرمون، خلل التوازن البكتيري.

Introduction

Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders in women of reproductive age, with prevalence reported to vary from 4% to 20% worldwide. With a multifaceted constellation of clinical features, PCOS chiefly presents as oligo- or anovulation, hyperandrogenism (clinical or biochemical), and polycystic ovarian morphology (PCOM) on ultrasound. The syndrome also encompasses significant metabolic disturbances, most notably insulin resistance (IR), obesity, and dyslipidemia, which cumulatively exacerbate reproductive dysfunction and introduce long-term cardiovascular risk [1]. Insulin resistance, a cornerstone of PCOS pathophysiology, frequently results in compensatory hyperinsulinemia, which synergistically worsens hyperandrogenemia via the stimulation of ovarian androgen secretion and the reduction of hepatic sex hormone-binding globulin (SHBG) production. These endocrine and metabolic disturbances infringe upon ovulatory function and fertility, typically causing menstrual dysregulation and an increased rate of miscarriage [2].

The PCOS burden extends from reproductive health to psychological wellbeing, presented commonly as depression or anxiety, and thereby its cumulative impact on quality of life. The syndrome's heterogeneity and multifactorial etiology, encompassing genes, environment, and lifestyle, make its clinical management an issue. New evidence has revealed a pivotal role of gut microbiota as an environmental controller that could regulate metabolic and endocrine parameters in PCOS. There are some research papers, primarily from Iran, that have demonstrated positive effects on insulin resistance and hormonal profiles following some probiotic, prebiotic, and symbiotic interventions in obese or overweight women with PCOS [3].

This article highlights the urgent need to better understand how the microbiome and hormones interact, calling for deeper mechanistic studies, targeted probiotic strategies, and large-scale research to confirm whether this microbiome–hormone connection can be effectively used in future therapy

Literate reviews

The human gut microbiota has increasingly been recognized as a critical regulator of hormonal balance, particularly in relation to reproductive and metabolic health. A growing body of research highlights the bidirectional communication between the gut and endocrine systems, where sex hormones influence gut microbial composition and, reciprocally, gut microbes contribute to hormonal modulation.

One of the foundational observations in this field is the sexually dimorphic nature of the gut microbiota and how it relates to metabolic outcomes. Kaliannan et al. (2018) demonstrated in a mouse model that estrogen modulates the gut microbiome, thereby influencing susceptibility to metabolic syndrome, which presents differently between sexes [2]. This relationship suggests that estrogen's protective metabolic effects may be, in part, microbiota-mediated.

Complementing these findings, Yoon et al. (2021) reviewed the broader roles of sex hormones in shaping gut microbiota composition, emphasizing how hormonal fluctuations across the lifespan, such as during puberty, menstruation, pregnancy, and menopause, can alter microbial diversity and function

[3]. These alterations may predispose individuals, particularly women, to disorders such as irritable bowel syndrome (IBS) and metabolic syndrome.

Pigrau et al. (2016) further deepened this understanding by discussing how stress, when combined with sex-specific hormonal profiles, influences the gut-brain-microbiota axis, potentially exacerbating gastrointestinal disorders like IBS [4]. Their work highlights the importance of considering both psychological and biological sex-based factors in gut health research.

More recently, Santos-Marcos et al. (2023) explored how sexual dimorphism in metabolic diseases is modulated by interactions between gut microbes and sex hormones [5]. Their findings underscore the microbiota's role in mediating gender differences in obesity, insulin resistance, and lipid metabolism.

Similarly, Siddiqui et al. (2022) focused on the gut microbiome's role in female-specific health conditions, such as polycystic ovary syndrome (PCOS) and endometriosis. The authors emphasized the therapeutic potential of microbiome modulation through diet or probiotics to restore hormonal balance in women [6].

Expanding on the intersection between gut microbiota and cardiometabolic health, Maffei et al. (2022) reviewed the crosstalk between microbiota and sex hormones in cardiovascular disease. They proposed that microbial metabolites such as short-chain fatty acids (SCFAs) and bile acids can interact with estrogen receptors and influence vascular function, adding another layer to cardiometabolic regulation [7].

Kumari et al. (2024) introduced the concept of phytoestrogens and their metabolism by gut bacteria, illustrating how certain microbial taxa are capable of converting dietary components into estrogen-like compounds that can influence systemic hormonal activity [8]. This highlights a novel mechanism through which diet and microbiota jointly impact hormonal health.

The therapeutic potential of this axis is evident in the work of Basnet et al. (2024), who reviewed the role of probiotics and prebiotics in modulating both the gut microbiome and hormone regulation. They proposed that specific strains of probiotics could improve hormonal profiles and reduce symptoms of metabolic and reproductive disorders [9].

Moreover, Pires et al. (2024) emphasized the emerging paradigm that positions the gut microbiota as an endocrine organ itself. Their review argued that microbial metabolites can act as signaling molecules with systemic hormonal effects, further reinforcing the need to consider gut health in hormonal disease management [10].

Material and Methods

This review was conducted to synthesize and evaluate current clinical evidence on the role of gut microbiota modulation, particularly through multi-strain probiotic supplementation, in managing endocrine and metabolic disturbances in women with polycystic ovary syndrome (PCOS). A systematic approach was used to identify peer-reviewed clinical studies published in English over the past decade. Relevant literature was retrieved from databases including PubMed, Scopus, and Web of Science using key terms such as “gut microbiota,” “probiotics,” “polycystic ovary syndrome,” “endocrine profile,” “BMI,” and “hormonal imbalance.” Inclusion criteria comprised randomized controlled trials (RCTs), observational studies, and meta-analyses that assessed the effects of probiotic interventions, specifically multi-strain formulations, on hormonal markers (e.g., TSH, SHBG, Free Androgen Index) and metabolic parameters such as body mass index in PCOS populations. Studies lacking control groups, insufficient outcome reporting, or those conducted on animal models were excluded.

Each included study was critically appraised for methodological rigor, sample size, study duration, strain-specificity of the probiotic intervention, and the presence or absence of gut microbiota profiling. Limitations related to heterogeneity in dosage, treatment duration, and probiotic strain composition were carefully noted. Furthermore, emphasis was placed on identifying whether studies incorporated mechanistic assessments such as metagenomic or metabolomic analyses to elucidate the microbiota, endocrine interaction. The synthesis aimed to highlight patterns, gaps, and future directions in this emerging field, with a focus on the therapeutic potential of targeted microbiota interventions in the management of PCOS.

Results and Discussion

Gut Microbiota and Sex Hormones:

Kaliannan et al. demonstrated that estrogen modulates gut microbiota composition in mice, influencing susceptibility to metabolic syndrome in a sex-specific manner [1]. Yoon et al. further reported that hormonal changes during puberty, pregnancy, and menopause significantly alter microbial diversity [2]. Pigrau et al. emphasized the impact of sex hormones on the gut-brain axis, especially under stress conditions, potentially exacerbating gastrointestinal disorders [3].

Metabolic and Endocrine Implications in PCOS:

Santos-Marcos et al. and Siddiqui et al. highlighted the sex-specific interactions between gut microbiota and metabolic syndrome, noting significant implications for insulin resistance and obesity in PCOS patients [4],[5]. Maffei et al. reviewed the role of microbial metabolites, such as SCFAs and bile acids, in cardiovascular health via estrogen receptor pathways [6].

Probiotic Interventions:

Kumari et al. and Basnet et al. explored the metabolism of phytoestrogens by gut bacteria and the role of probiotics in hormonal regulation, respectively [7],[8]. Pires et al. posited that gut microbiota functions as an endocrine organ due to its production of hormone-like metabolites [9].

Clinical Evidence on Probiotic Supplementation in PCOS:

Clinical trials have shown promising outcomes with specific probiotic strains:

Guevara et al. found that L. acidophilus and B. lactis improved insulin sensitivity and reduced testosterone levels [10].

Li et al. demonstrated improvements in SHBG and free androgen index following L. rhamnosus and B. breve supplementation [11].

Tabrizi et al.'s meta-analysis reported improved lipid profiles after probiotic intervention [12].

Kaur et al. observed reduced androgen levels and better insulin resistance with L. casei and B. longum [13].

Ramzan et al. noted modest benefits from multi-strain probiotics but emphasized the importance of strain specificity and dosage [14].

The findings suggest a multifaceted role of gut microbiota in modulating hormonal and metabolic outcomes in PCOS. Probiotic interventions, particularly multi-strain formulations, appear effective in improving endocrine function. However, heterogeneity in study design, probiotic strains, and treatment duration limits generalizability. The therapeutic mechanism likely involves SCFA production, improved gut barrier function, and estrogen receptor modulation.

The Effects of Probiotic interventions in Women with PCOS

This review compiles evidence on the effects of probiotic interventions on hormonal and metabolic factors in women with PCOS, summarized in Table 1.

Table 1. Summary of Probiotic Interventions in Women with PCOS.

Ref.	Authors	Sample Size	Probiotic Strains	Duration	Main Findings
[10]	Guevara et al., 2024	60	L. acidophilus, B. lactis	12 weeks	Improved insulin sensitivity, reduced testosterone
[11]	Li et al., 2021	50	L. rhamnosus, B. breve	8 weeks	Reduced inflammation, improved SHBG and FAI
[12]	Tabrizi et al., 2019	45	Mixed strains	12 weeks	Improved lipid profiles (↓ triglycerides, ↓ LDL-C)
[13]	Kaur et al., 2022	72	L. casei, B. longum	10 weeks	Reduced androgen levels, improved insulin resistance
[14]	Ramzan et al., 2024	40	Multi-strain (not specified)	6 weeks	Modest effect; strain selection and dosage heterogeneity limit interpretation

Insulin Resistance

The evidence indicates that probiotic supplementation may improve insulin resistance in women with PCOS (Guevara et al., 2024; Li et al., 2021) [1],[2]. This is a critical finding, as insulin resistance is a central feature of PCOS, contributing to hyperandrogenism and ovulatory dysfunction. The proposed mechanism involves the modulation of the gut microbiota, which can influence glucose metabolism and reduce systemic inflammation. Certain bacterial strains may enhance insulin sensitivity by producing short-chain fatty acids like butyrate, which have been shown to improve glucose homeostasis [3], [4].

Hormonal Modulation

The table suggests that probiotics may help reduce reproductive hormone levels, particularly androgens like testosterone. While direct evidence is still emerging, the improvement in insulin sensitivity may play a key role. Decreased insulin resistance can lead to reduced androgen production by the ovaries, potentially restoring hormonal balance (Kaur et al., 2022) [5]. The gut microbiota's ability to influence estrogen metabolism may also contribute to hormonal regulation in PCOS [6].

Lipid Profiles

Improvements in lipid profiles, such as reductions in cholesterol and triglycerides, were also noted with probiotic interventions [1],[3]. Gut microbiota can modulate lipid metabolism through various

mechanisms, including influencing bile acid metabolism and reducing the absorption of dietary fats. This can have a positive impact on cardiovascular risk factors associated with PCOS [4].

Inflammation

PCOS is often associated with chronic low-grade inflammation, which can exacerbate insulin resistance and contribute to other metabolic complications. Probiotics may help reduce inflammation by improving gut barrier function and reducing the translocation of inflammatory molecules (Li et al., 2021) [2]. Certain probiotic strains can promote the growth of beneficial bacteria that produce anti-inflammatory compounds, such as SCFAs, and suppress the growth of harmful bacteria that produce pro-inflammatory substances [3], [6].

Strengths and Limitations

While the evidence is promising, it's important to consider the limitations. Many studies have small sample sizes and varying methodologies, making it difficult to draw definitive conclusions. Additionally, the specific strains of probiotics used, dosages, and duration of interventions vary across studies, which may influence the outcomes. More research is needed to determine the optimal probiotic formulations and treatment protocols for PCOS (Ramzan et al., 2024) [1], [7].

Future Research Directions

Identifying specific probiotic strains that are most effective for PCOS.

Investigating the mechanisms by which probiotics exert their effects on hormonal and metabolic profiles.

Conducting larger, well-designed clinical trials with standardized protocols.

Assessing the long-term effects of probiotic interventions on PCOS outcomes, including fertility and cardiovascular health.

Conclusion

Women experience autoimmune and inflammatory diseases more frequently than men, a disparity potentially linked to hormonal fluctuations during puberty, pregnancy, and menopause. Polycystic Ovary Syndrome, a prevalent endocrine disorder, significantly impacts women's reproductive health and overall well-being. The intricate interplay between the gut microbiota and the host's physiology has garnered significant attention, particularly in the context of women's health, where hormonal fluctuations exert a profound influence.

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