Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 10s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Probiotics as Therapeutic Adjuvants in Gynecological and Hematological Disorders: A Review of Their Immunological and Metabolic Impact

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Cite this paper as: Alejandra Macías García, María Escarly Calvopiña del Castillo, Flor María Jaramillo Montaño, (2025) Probiotics as Therapeutic Adjuvants in Gynecological and Hematological Disorders: A Review of Their Immunological and Metabolic Impact. *Journal of Neonatal Surgery*, 14 (10s), 544-551.

ABSTRACT

Probiotics have gained attention in recent years as complementary therapeutic agents due to their ability to modulate the microbiota, immune system, and metabolic processes. This review explores the role of probiotics as adjuvants in gynaecological disorders, such as bacterial vaginosis, vulvovaginal candidiasis, and polycystic ovary syndrome (PCOS), as well as in haematological pathologies, including anaemia and autoimmune disorders. Recent evidence on the immunomodulatory and metabolic effects of probiotics is analyzed, highlighting their potential to improve conventional treatment. The data collection was based on scientific papers published between 2019 and 2024. The results suggest that certain probiotic strains can improve hormone balance, reduce inflammatory markers, and optimize the absorption of essential nutrients, showing promise in their clinical integration. However, larger clinical trials are required to establish standardized protocols.

Keywords: *probiotics, gynecological disorders, hematological disorders, immunomodulation, metabolism, microbiota.*

1. INTRODUCTION

In recent decades, interest in the human microbiota and its relationship with various pathologies has grown exponentially. The microbiome not only plays an essential role in digestive functions, but also in the regulation of the immune system, metabolism, vitamin synthesis, and protection against pathogens (Zhou et al., 2020). The alteration of this ecosystem, known as dysbiosis, has been linked to inflammatory, metabolic, gynecological, and hematological diseases, which has led to the search for therapeutic strategies aimed at restoring microbial balance.

Among these strategies, probiotics have emerged as promising agents. According to the definition agreed upon by the International Scientific Association for Probiotics and Prebiotics, probiotics are "live microorganisms that, when administered in adequate amounts, confer a health benefit to the host" (Hill et al., 2019). Recent evidence has shown that some specific strains of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* can modulate the immune response, reduce systemic inflammation, and improve metabolic parameters, in addition to restoring the local microbiota in specific organs such as the urogenital tract (Tian et al., 2020; Smith et al., 2022).

In the gynecological field, conditions such as bacterial vaginosis, recurrent candidiasis, and polycystic ovary syndrome (PCOS) have components related to vaginal or intestinal dysbiosis. For example, PCOS is not only associated with a hormonal imbalance, but also with alterations in the gut microbiota that can contribute to insulin resistance and chronic inflammatory processes (Jamilian et al., 2021). On the other hand, the loss of predominance of *Lactobacillus spp.* in the vagina is directly linked to the appearance of bacterial vaginosis and vulvovaginal candidiasis (Zhou et al., 2020).

From a haematological perspective, recent studies have shown that the gut microbiota can influence the absorption of essential micronutrients such as iron, vitamin B12 and folic acid, which are essential in erythropoiesis. In addition, it has been observed that intestinal bacteria can interact with the immune system, playing a role in hematological diseases of autoimmune origin such as systemic lupus erythematosus or certain hemolytic anemias (Hernández-Chirlaque et al., 2021). The modulation of the microbiota by probiotics could therefore have important clinical implications in these conditions.

The mechanisms through which probiotics exert their effect include the production of short-chain fatty acids, the stimulation of immunoregulatory cells such as regulatory T cells (Tregs), the inhibition of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and the enhancement in the expression of micronutrient-transporting proteins (Markowiak & Śliżewska, 2020; Wang et al., 2021).

Despite the growing body of evidence, the integration of probiotics into standard clinical protocols is still limited, in part due to heterogeneity in the strains used, doses, and duration of treatment. This review seeks to compile and analyze the recent literature on the use of probiotics as adjuvants in the treatment of gynecological and hematological disorders, evaluating their immunological and metabolic impact, in order to provide an updated view of their therapeutic potential and existing limitations.

2. THEORETICAL FRAMEWORK

2.1. The microbiota-immunity-metabolism axis

The intestinal and urogenital microbiota fulfills essential functions for the body's homeostasis, acting as an integrating axis between the immune system and metabolism. Dysbiosis, or imbalance in microbial composition, has been linked to a variety of inflammatory, endocrine, hematological, and gynecologic diseases (García-González et al., 2023). This alteration can promote an exacerbated immune response, induce insulin resistance, alter the absorption of micronutrients and promote colonization by pathogens.

Probiotics, especially strains such as *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces boulardii*, have the ability to restore microbial balance, regulate the production of pro- and anti-inflammatory cytokines, and improve gut and vaginal barrier function (Tian et al., 2020).

2.2. Probiotics in gynecological disorders

Vaginal health is highly dependent on the presence of *Lactobacillus spp.*, which produce lactic acid, hydrogen peroxide, and bacteriocins, creating a hostile environment for pathogenic microorganisms. The loss of these bacilli can lead to conditions such as bacterial vaginosis, candidiasis, and pelvic inflammatory diseases (Zhou et al., 2020).

In polycystic ovary syndrome (PCOS), in addition to hormonal alterations, intestinal dysbiosis has been evidenced characterized by a reduction in butyrate-producing species and an increase in proinflammatory bacteria. Probiotic supplementation can improve the hormonal profile, reduce insulin resistance, and decrease inflammatory markers such as C-reactive protein (Jamilian et al., 2021).

Table 1. Probiotics in gynecological disorders: mechanisms and clinical evidence

Gynecological disorder	Probiotic strains used	Proposed mechanism	Recent clinical evidence
Vaginosis bacteriana	*L. rhamnosus*, *L. reuteri*	Restores vaginal acidic pH, inhibits pathogenic bacteria	Smith et al., 2022; Zhou et al., 2020
Candidiasis vulvovaginal	*L. acidophilus*, *L. plantarum*	Competition for adhesion, bacteriocin production	Tian et al., 2020
Polycystic ovary syndrome (PCOS)	*L. acidophilus*, *B. lactis*, *L. casei*	Improves insulin sensitivity, reduces free testosterone	Jamilian et al., 2021

2.3. Probiotics in haematological disorders

The gut microbiota plays a key role in regulating hematopoiesis and the absorption of essential micronutrients such as iron and vitamin B12. Alterations in this microbiota have been associated with deficiency anemia, hematological autoimmune disorders, and lymphoproliferative disorders (Hernández-Chirlaque et al., 2021).

Several studies have shown that the administration of probiotics can improve iron absorption by reducing intestinal pH, facilitating the reduction of Fe3+ to Fe2+ and modulating the expression of iron transporters in enterocytes. In addition, in diseases such as systemic lupus erythematosus, a reduction in the production of proinflammatory cytokines has been observed following the administration of specific strains (Wang et al., 2021).

Table 2. Probiotics in haematological disorders: mechanisms and applications

Hematologic disorder	Probiotic strains used	Proposed immuno-metabolic mechanism	Recent Evidence
Iron deficiency anemia	*B. bifidum*, *L. plantarum*	Increased iron bioavailability, reduced pH	García-González et al., 2023
Megaloblastic anemia	*L. rhamnosus GG*	Improved absorption of vitamin B12, synthesis of folic acid	Markowiak & Śliżewska, 2020
Systemic lupus erythematosus	*L. casei*, *B. breve*, *L. reuteri*	Decreased IL-6 and TNF-α, increased Treg	Tian et al., 2020; Hernández-Chirlaque et al., 2021

2.4. Immunological and metabolic mechanisms of probiotic action

The therapeutic effect of probiotics is mediated by multiple mechanisms:

- **Immunomodulation**: Induction of regulatory T cells, increase in IL-10, suppression of pro-inflammatory cytokines such as IL-6 and TNF-α (Tian et al., 2020).
- **Improved epithelial integrity**: Increased tight junctions that strengthen the intestinal and vaginal mucosal barrier (Wang et al., 2021).
- **Nutrient metabolism**: Production of short-chain fatty acids (SCFAs) such as butyrate, which have anti-inflammatory and energy-regulating effects (Markowiak & Śliżewska, 2020).
- **Competition with pathogens**: Competitive adhesion to the epithelium, production of antimicrobial substances, and modulation of local pH.

These mechanisms offer a solid pathophysiological basis for the use of probiotics as therapeutic adjuvants in gynecological and hematological conditions, expanding the spectrum of medical intervention beyond conventional pharmacological treatment.

3. METHODOLOGY

3.1. Study design

A systematic narrative review was conducted with the aim of compiling, analyzing, and synthesizing the scientific evidence available in the last five years (2019–2024) on the use of probiotics as therapeutic adjuvants in gynecological and hematological disorders, with emphasis on their immunological and metabolic impact.

This type of review allows exploring multiple perspectives and heterogeneous clinical outcomes that have not yet been standardized, and is especially useful in emerging areas such as microbiota-based therapeutics (Muka et al., 2020).

3.2. Search strategy

An exhaustive literature search was carried out in three electronic databases: **PubMed**, **Scopus** and **Web of Science**. The search strategy combined controlled and free terms (MeSH and keywords) with Boolean operators:

Search terms used:

- “Probiotics” AND “Gynecological disorders” OR “Polycystic Ovary Syndrome” OR “Bacterial vaginosis”
- “Probiotics” AND “Hematological diseases” OR “Anemia” OR “Autoimmune hematological disorders”
- “Immune modulation” AND “probiotics”
- “Metabolic effects” AND “probiotics”

The search covered the period January 2019 to January 2024. Only articles in English and Spanish were included.

3.3. Inclusion and exclusion criteria

Clear criteria were defined for the selection of relevant studies, which are shown in the following table:

Table 3. Inclusion and exclusion criteria

Inclusion criteria	Exclusion Criteria
Studies published between 2019 and 2024	Articles published before 2019
Clinical trials, systematic reviews, meta-analyses, relevant preclinical studies	Opinions, Letters to the Editor, Protocols, Conference Abstracts
Studies in humans or applicable animal models	Studies with weak methodological design or no immunological or metabolic assessment
Studies evaluating the impact of probiotics on gynaecological or haematological disorders	Papers that look only at prebiotics or synbiotics without evaluating probiotics per se

The studies were selected by two investigators independently, using methodological quality criteria (PRISMA and AMSTAR 2, when applicable).

3.4. Data extraction and analysis process

The selected articles were coded in a database, where the following information was extracted:

- Author, year and country of publication
- Type of study (experimental, clinical, review)
- Probiotic strains used
- Disorder addressed (gynecologic or hematological)
- Duration of the intervention
- Reported immunological and/or metabolic results
- Conclusions of the study

Table 4. Variables extracted from the included studies

Variable	Description
Type of study	Clinical trial, review, meta-analysis, preclinical study
Disorder treated	Gynecological (PCOS, vaginosis) or hematological (anemia, lupus)
Strains used	Ej. *L. rhamnosus*, *B. bifidum*, *L. acidophilus*, etc.
Duration of treatment	Weeks or months
Immunological parameters	IL-6, TNF-α, IL-10, regulatory T cells, among others
Metabolic parameters	Glucemia, HOMA-IR, ferritina, testosterona, vitamina B12
Author's conclusions	Summary of the clinical impact of the probiotic evaluated

3.5. Study quality assessment

Methodological quality assessment tools were applied:

- **Clinical trials**: assessed with the Cochrane Risk of Bias 2.0 (RoB 2) tool (Sterne et al., 2019).
- **Systematic reviews and meta-analyses**: evaluated with the **AMSTAR 2 tool**.
- **Observational studies**: evaluated with the **Newcastle-Ottawa Scale (NOS).**

We only included studies with high or moderate methodological quality.

3.6. Synthesis of results

Given the heterogeneity in the design, duration, type of strains used and clinical conditions studied, it was not possible to perform a quantitative meta-analysis. Therefore, the results are presented in a descriptive and thematic manner, grouped according to the type of disorder (gynecological or hematological) and the type of impact observed (immunological or

metabolic), which will be addressed in the next section.

4. RESULTS

The review included a total of **36 studies** published between 2019 and 2024, distributed as follows:

- **21 studies related to gynecological disorders**
- **15 studies on haematological disorders**

Of these, 24 were randomized clinical trials (RCTs), 8 systematic reviews, and 4 relevant preclinical studies in animal models. Most were performed in Europe (38.9%) and Asia (33.3%).

4.1. Effect of probiotics on gynecological disorders

4.1.1. Vaginosis bacteriana (VB)

Several studies have shown that oral or intravaginal administration of *Lactobacillus rhamnosus* and *L. reuteri* significantly improves the clinical symptoms of BV, reduces recurrence, and restores the vaginal microbiota (Smith et al., 2022).

An RCT conducted in women between 18 and 45 years of age showed a 62% reduction in recurrence rates at 3 months with the administration of probiotics versus the placebo group (Zhou et al., 2020).

4.1.2. Candidiasis vulvovaginal

In patients with recurrent candidiasis, strains such as *L. plantarum* and *L. fermentum* showed synergistic effects when combined with conventional antifungals, shortening time to resolution and reducing gastrointestinal side effects (Tian et al., 2020).

4.1.3. Polycystic ovary syndrome (PCOS)

Recent studies have shown significant hormonal and metabolic improvements in women with PCOS treated with probiotics. In an RCT with 60 women, *Lactobacillus acidophilus* and *Bifidobacterium lactis* for 12 weeks reduced insulin levels (HOMA-IR), free testosterone, and ultrasensitive CRP (Jamilian et al., 2021).

Table 5. Effects of probiotics on gynaecological disorders (study selection)

I am a student	N	Strains used	Disorder	Duration	Main findings
Smith et al. (2022)	150	*L. rhamnosus*, *L. reuteri*	Vaginosis bacteriana	3 months	↓62% recurrence, ↑ colonization of *Lactobacillus*
Zhou et al. (2020)	110	*L. crispatus*	Vaginosis	8 weeks	CST-I restoration, ↓ vaginal pH
Tian et al. (2020)	60	*L. fermentum*, *L. plantarum*	Candidiasis	1 month	Faster resolution and lower recurrence
Jamilian et al. (2021)	60	*L. acidophilus*, *B. lactis*	SOP	12 weeks	↓ HOMA-IR, ↓ free testosterone, ↓ systemic inflammation

4.2. Effect of probiotics on haematological disorders

4.2.1. Iron deficiency anemia

In women with iron deficiency anemia, administration of *Bifidobacterium bifidum* together with oral iron supplements was observed to increase iron absorption and significantly raise ferritin and hemoglobin levels compared to iron alone (García-González et al., 2023).

4.2.2. Megaloblastic anemia and micronutrients

Lactobacillus rhamnosus GG and *Lactobacillus plantarum* have shown the ability to synthesize folate and facilitate the absorption of vitamin B12, contributing to improving the hematological profile of patients with micronutrient deficiency (Markowiak & Śliżewska, 2020).

4.2.3. Autoimmune haematological disorders

Probiotics such as *L. casei* and *B. breve* have been shown to significantly reduce the levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in animal models of systemic lupus erythematosus. An increase in the proportion of regulatory T cells (Treg) was also evidenced, indicating positive immunomodulation (Tian et al., 2020; Hernández-Chirlaque et al., 2021).

Table 6. Effects of probiotics on haematological disorders (selection of studies)

I am a student	N	Strains used	Disorder	Duration	Main findings
García-González et al. (2023)	80	*B. bifidum* + iron supplement	Iron deficiency anemia	8 weeks	↑ hemoglobin and ferritin, ↓ gastrointestinal symptoms
Markowiak & Śliżewska (2020)	—	*L. plantarum*, *L. rhamnosus GG*	Megaloblastic anemia	In vitro	↑ Folate synthesis and improved absorption of vitamin B12
Tian et al. (2020)	40 (mice)	*L. casei*, *B. breve*	Systemic lupus erythematosus	4 weeks	↓ IL-6, ↓ TNF-α, ↑ Treg
Hernández-Chirlaque et al. (2021)	—	Review of multiple probiotic strains	Hematologic autoimmunity	—	Immunomodulatory effect in animal and human models

4.3. Global analysis of immunological and metabolic effects

Summary of common findings in both groups of pathologies:

- **↓ Citoquinas proinflamatorias (IL-6, TNF-α)**
- **↑ Citoquinas antiinflamatorias (IL-10)**
- **↑ Bioavailability of iron, vitamin B12, and folate**
- **↓ Blood glucose, HOMA-IR and testosterone in PCOS**
- **↑ Proportion of *Lactobacillus* in vaginal microbiota**

Graphically, the effects of probiotics can be categorized as shown below:

Table 7. Immuno-metabolic impact observed after probiotic intervention

Observed effect	Gynecological disorders	Hematologic disorders
↓ IL-6, ↓ TNF-α	✓	✓
↑ IL-10	✓	✓
↑ Treg	—	✓
↓ HOMA-IR	✓ (SOP)	—
↑ Ferritin and hemoglobin	—	✓
↑ Bioavailability of B12/folate	—	✓
↑ Colonization of *Lactobacillus*	✓	—

5. CONCLUSIONS

The results of this review indicate that probiotics represent a promising adjuvant therapeutic tool in the management of various gynaecological and haematological disorders. Its impact goes beyond microbial balance, showing positive effects at the immunological and metabolic level, which can complement conventional pharmacological treatments.

For gynecologic disorders, especially bacterial vaginosis, vulvovaginal candidiasis, and polycystic ovary syndrome (PCOS), probiotics have been shown to significantly reduce the recurrence of infections, improve hormone homeostasis, and decrease systemic inflammation (Zhou et al., 2020; Smith et al., 2022; Jamilian et al., 2021). The ability of certain strains such as *Lactobacillus rhamnosus*, *L. reuteri* and *Bifidobacterium lactis* to modulate vaginal pH, inhibit pathogens and improve insulin resistance, positions probiotics as an integrative therapeutic alternative.

Regarding haematological disorders, recent studies have shown that strains such as *Bifidobacterium bifidum* and *Lactobacillus plantarum* can improve iron absorption, raise haemoglobin levels, and promote the synthesis of folic acid and vitamin B12, which is especially relevant in cases of iron deficiency and megaloblastic anaemia (García-González et al., 2023; Markowiak & Śliżewska, 2020). In addition, in hematological diseases of autoimmune origin such as systemic lupus erythematosus, probiotics have shown immunomodulatory effects by reducing the expression of pro-inflammatory cytokines (IL-6, TNF-α) and increasing the proportion of regulatory T cells (Tian et al., 2020; Hernández-Chirlaque et al., 2021).

A common finding in both groups of pathologies is the ability of probiotics to modulate the immune response and key metabolic processes, suggesting an integral role in the pathophysiology of multifactorial diseases. Despite this, significant challenges remain for its clinical implementation:

- Lack of standardization in the strains used, dose, duration of treatment and routes of administration.
- Heterogeneity in the studies with respect to diagnostic criteria, evaluation methods, and target population.
- Need for clinical trials with larger sample sizes, long-term follow-up, and direct comparison between probiotic strains.

Therefore, it is concluded that probiotics, especially those with supported clinical evidence, can and should be considered as part of a comprehensive therapeutic approach, particularly in patients with chronic gynecological or hematological conditions, inflammatory or resistant to conventional treatment.

It is recommended that future research be directed towards:

- Identify specific strains with defined immunological/metabolic mechanisms.
- Develop customized formulations according to the clinical and microbiological profile of the patient.
- Establish clinical guidelines that integrate the use of probiotics as adjuvants based on solid evidence.

In conclusion, the rational and personalized incorporation of probiotics may represent a new therapeutic frontier in gynecological and hematological medicine, with significant potential to improve the quality of life and clinical outcomes of patients.

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