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# Estrobolome, gut microbiota and estrogen dependent diseases:

## endocrine immunemetabolic integration and new translational frontiers

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This review therefore aims to integrate current mechanistic and clinical evidence linking the estrobolome to estrogen dependent diseases, while also exploring emerging translational strategies for microbiome targeted interventions.

## INTRODUCTION

Contemporary medicine is undergoing a significant conceptual transformation as it recognizes that physiological systems traditionally studied in isolation are deeply interconnected. Among these interconnections, the interface between the gut microbiota and hormonal metabolism stands out as one of the most promising translational frontiers.

For decades, estrogen metabolism was understood predominantly from ovarian, hepatic and peripheral perspectives. However, the recognition that intestinal microorganisms actively participate in modulating the enterohepatic recirculation of estrogens has redefined the understanding of this system. The **estrobolome**, a functional subset of the microbiome responsible for this modulation, represents a concrete biochemical link between microbial ecology and systemic endocrinology.

This integration becomes particularly relevant in conditions in which estrogen plays a central role in pathophysiology, such as polycystic ovary syndrome, endometriosis and lipedema. In these diseases, chronic low grade inflammation, metabolic resistance and hormonal dysregulation coexist within a dynamic network. The gut microbiota emerges as a key modulator of this network.

## CHAPTER 1: THE ESTROBOLOME

### Molecular Foundations and Scientific Consolidation

The term **estrobolome** was introduced by Plottel and Blaser to describe the set of microbial genes capable of metabolizing estrogens in the gastrointestinal tract. Unlike taxonomic classifications based on specific species, the estrobolome is a **functional concept**, defined by the collective enzymatic capacity of the microbial community.

This distinction is central. The clinical impact does not depend exclusively on the presence of specific bacterial genera, but on the **functional expression of enzymes**, including:

- β glucuronidases
- Sulfatases
- Bacterial hydroxysteroid dehydrogenases
- Enzymes involved in the metabolism of lignans and phytoestrogens

The concept of the estrobolome, understood as the set of intestinal microorganisms capable of metabolizing estrogens, has gained clearer conceptual definition over the past decade. Review and mechanistic synthesis studies have highlighted that specific intestinal bacteria produce enzymes such as β glucuronidase capable of deconjugating estrogens previously metabolized in the liver, allowing their reabsorption through enterohepatic circulation.

This process directly influences systemic estrogen availability and may impact several physiological and pathological processes dependent on this hormone. Conceptual synthesis works published by **Shapira (2016)** and **Baker et al. (2017)** consolidated the idea that gut microbiota composition plays a relevant role in modulating estrogen metabolism, opening new avenues for investigating the relationship between intestinal dysbiosis, hormonal alterations and estrogen dependent diseases.

Systemic estrogen metabolism follows **five interdependent stages**:

Ovarian and peripheral synthesis of estradiol and estrone

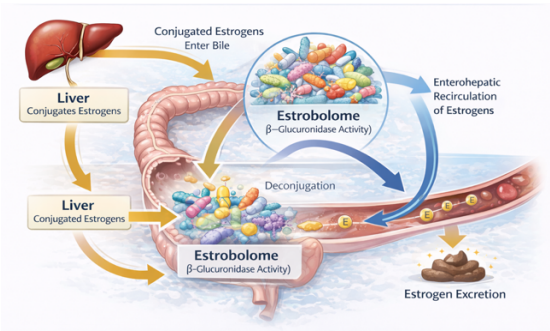
Hepatic conjugation through glucuronidation and sulfation

Biliary excretion of conjugated estrogens

Intestinal deconjugation mediated by bacterial enzymes

Reabsorption and enterohepatic recirculation

Figure 1. Estrogen metabolism and the role of the estrobolome.




The intestinal stage represents a critical modulation point. β glucuronidase activity determines the fraction of estrogen that returns to systemic circulation in its active form. This recirculation influences prolonged tissue exposure to estrogens, particularly in sensitive organs such as ovaries, endometrium and adipose tissue.

An important conceptual clarification is that the estrobolome should not be interpreted as a fixed taxonomic group, but rather as a functional collection of microbial genes capable of metabolizing estrogens. The presence of specific bacterial genera alone does not necessarily determine estrobolome activity, since enzymatic capacity, gene expression and host factors can substantially influence estrogen deconjugation and enterohepatic recirculation. Consequently, interindividual variability in microbiome composition and metabolic activity represents a critical determinant of estrogen exposure and may partly explain the heterogeneous clinical manifestations observed across estrogen dependent diseases.

## CHAPTER 2: Gut Microbiota, Inflammation and Estrogen Dependent Diseases

The interaction between gut microbiota and endocrine metabolism does not occur in isolation. On the contrary, it is integrated within a complex network involving immune signaling, intestinal barrier integrity, metabolic regulation and systemic inflammatory responses.

The intestinal mucosa represents one of the largest immunological interfaces in the human body. Trillions of microorganisms coexist with epithelial and immune cells in a dynamic balance that, under physiological conditions, maintains metabolic homeostasis and immunological tolerance. However, disturbances in this ecosystem may lead to dysbiosis, increased intestinal permeability and systemic inflammatory activation.

The phenomenon popularly referred to as **"leaky gut"**, described by Fasano (2012), illustrates how alterations in intestinal barrier integrity allow microbial components such as lipopolysaccharides to translocate into the circulation. This process triggers activation of innate immune receptors and promotes a chronic low grade inflammatory state.

Chronic inflammation is increasingly recognized as a central element in the pathogenesis of multiple estrogen dependent diseases. In this context, intestinal dysbiosis may influence hormonal signaling both directly, through enzymatic modulation of estrogen metabolism, and indirectly, through inflammatory and metabolic pathways.

Figure 2. Integrative model of the estrobolome axis and estrogen dependent diseases.

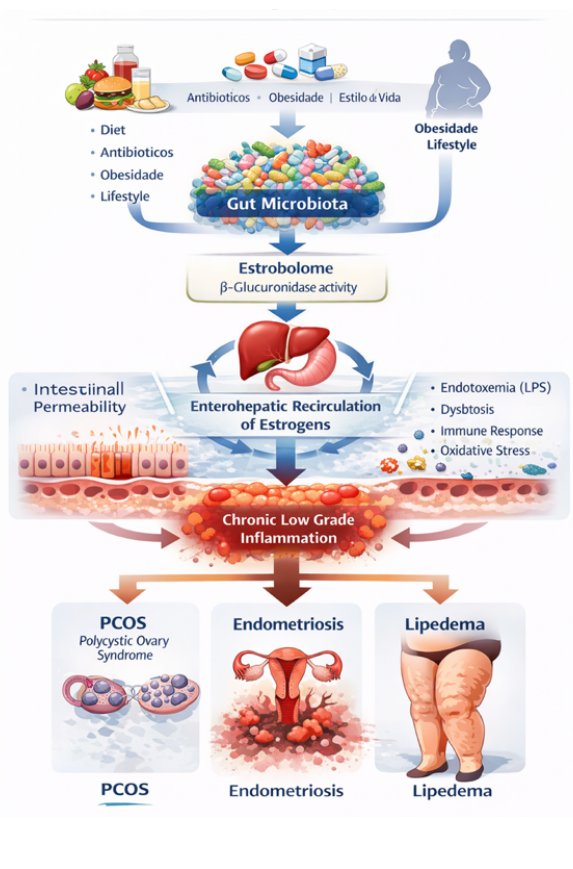



Figure 2. Integrative model of the estrobolome axis linking gut microbiota, intestinal barrier function and estrogen dependent diseases. Gut microbial enzymes, particularly β glucuronidases and sulfatases, can deconjugate estrogen metabolites excreted in bile, allowing their reabsorption through enterohepatic circulation. Dysbiosis, intestinal permeability and chronic low grade inflammation may alter this regulatory axis, influencing systemic estrogen exposure and potentially contributing to the pathophysiology of conditions such as polycystic ovary syndrome, endometriosis and other hormone related disorders.

Short chain fatty acids produced by microbial fermentation of dietary fibers represent another important regulatory mechanism. Compounds such as acetate, propionate and butyrate exert immunomodulatory effects, influence insulin sensitivity and participate in epigenetic regulation through histone deacetylase inhibition.

Therefore, the microbiota should not be viewed merely as a collection of microorganisms, but as a metabolically active endocrine organ capable of producing signaling molecules that influence distant physiological systems.

## CHAPTER 3: Polycystic Ovary Syndrome and the Microbiota Hormonal Axis

Polycystic ovary syndrome represents one of the most prevalent endocrine disorders in women of reproductive age, affecting approximately 8 to 13 percent of the female population worldwide. The condition is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology, frequently accompanied by insulin resistance and chronic low grade inflammation.

Recent research has highlighted the potential role of the gut microbiota in the pathophysiology of this syndrome. Tremellen and Pearce (2012) were among the first to propose that dysbiosis could contribute to the metabolic and inflammatory alterations observed in patients with polycystic ovary syndrome.

Subsequent investigations have reinforced this hypothesis. Systematic reviews and meta analyses have identified significant alterations in microbial diversity and composition in affected women, suggesting that intestinal dysbiosis may influence metabolic regulation, inflammatory signaling and hormonal balance.

Experimental models have also provided mechanistic insights. Qi et al. (2019) demonstrated that the gut microbiota bile acid interleukin 22 axis may play a relevant role in the development of polycystic ovary syndrome, highlighting the complex interaction between microbial metabolism, immune signaling and endocrine regulation.

Clinical trials investigating probiotic supplementation have produced promising results. Meta analyses of randomized controlled trials suggest that specific probiotic interventions may improve metabolic parameters, insulin resistance and inflammatory markers in women with polycystic ovary syndrome.

Although the field remains under active investigation, these findings support the hypothesis that microbiota modulation may represent a complementary therapeutic strategy in the management of this complex condition.

## CHAPTER 4: Endometriosis, Microbiota and Estrogen Signaling

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial like tissue outside the uterine cavity. The condition affects millions of women worldwide and is frequently associated with pelvic pain, infertility and reduced quality of life.

Although the exact mechanisms underlying endometriosis remain incompletely understood, increasing evidence suggests that immune dysfunction, hormonal imbalance and inflammatory activation play central roles in disease progression.

Recent studies have also begun to explore the potential contribution of the microbiota. Systematic reviews have indicated that both intestinal and reproductive tract microbial communities may be altered in women with endometriosis.

A particularly intriguing finding emerged from investigations demonstrating the presence of Fusobacterium species in endometriotic lesions. Research published in 2023 in *Science Translational Medicine* reported that infection with *Fusobacterium nucleatum* may promote endometriosis development through phenotypic changes in endometrial fibroblasts.

These findings suggest that microbial signals may interact with host cellular pathways involved in inflammation, fibrosis and tissue remodeling. Although further studies are required to confirm these mechanisms, the results reinforce the concept that microbial ecosystems may influence disease progression in ways that extend beyond classical endocrine regulation.

Understanding these interactions may open new opportunities for non invasive diagnostic strategies and microbiome targeted therapies in endometriosis.

## CHAPTER 5: Lipedema, Adipose Tissue and Microbial Modulation

Lipedema is a chronic adipose tissue disorder characterized by symmetrical accumulation of subcutaneous fat, predominantly in the lower limbs, frequently accompanied by pain, edema and increased capillary fragility. Although historically underdiagnosed, the condition has gained increasing attention within the fields of vascular medicine, endocrinology and metabolic research.

Unlike classical obesity, lipedema presents distinct pathophysiological characteristics. Patients frequently exhibit disproportionate fat distribution, resistance to conventional weight loss strategies and signs of lymphatic dysfunction. These characteristics suggest that the disorder involves complex alterations in adipose tissue biology rather than merely caloric imbalance.

Emerging evidence indicates that chronic inflammation and microvascular alterations may play central roles in lipedema development. Histological analyses have demonstrated dilated lymphatic microvessels, endothelial dysfunction and infiltration of inflammatory cells within affected adipose tissue.

Although research on the relationship between lipedema and the gut microbiota remains in early stages, several mechanistic pathways suggest possible interactions. Microbial metabolites, inflammatory mediators and hormonal signals derived from intestinal ecosystems may influence adipose tissue metabolism, vascular permeability and systemic inflammatory tone.

Given that estrogens exert significant influence on adipose tissue distribution and vascular function, the interaction between the estrobolome and estrogen metabolism may represent an additional dimension in understanding the pathophysiology of lipedema.

Further investigation is required to clarify these relationships, but the integration of microbiome science with adipose tissue biology may provide valuable insights for future therapeutic strategies.

## CHAPTER 6: Microbiota, Metabolism and Systemic Energy Regulation

The relationship between gut microbiota and metabolic regulation has been extensively investigated over the past two decades. Early landmark studies demonstrated that alterations in microbial composition may influence energy extraction from the diet, host metabolism and body weight regulation.

Research conducted by Turnbaugh et al. (2006) revealed that the microbiome associated with obesity exhibits increased capacity for energy harvest, suggesting that microbial communities may influence metabolic efficiency and nutrient utilization.

Subsequent investigations expanded this perspective by identifying specific microbial metabolites capable of influencing host metabolic pathways. Among these metabolites, short chain fatty acids have received particular attention due to their role in regulating insulin sensitivity, appetite signaling and energy homeostasis.

Butyrate, propionate and acetate act not only as energy substrates but also as signaling molecules capable of interacting with host receptors and modulating inflammatory pathways. These metabolites influence metabolic processes in the liver, adipose tissue and skeletal muscle.

The microbiota also contributes to bile acid metabolism, generating secondary bile acids that act as ligands for nuclear receptors involved in glucose and lipid metabolism. This interaction establishes an additional communication axis between intestinal microorganisms and host metabolic regulation.

Collectively, these mechanisms reinforce the concept that the microbiota functions as an important regulator of systemic metabolism, influencing pathways that intersect with hormonal and inflammatory processes.

## CHAPTER 7: Next Generation Probiotics and Microbiome Based Therapeutics

As the understanding of host microbiota interactions advances, the concept of probiotics has also evolved. Traditional probiotic approaches focused primarily on the administration of live microorganisms with general health benefits. However, recent developments have introduced the concept of next generation probiotics, which emphasizes defined microbial strains with specific mechanistic functions.

Next generation probiotics include microorganisms selected based on their metabolic capabilities, immunomodulatory properties and ability to interact with host signaling pathways. This approach seeks to move beyond empirical supplementation toward targeted microbiome modulation.

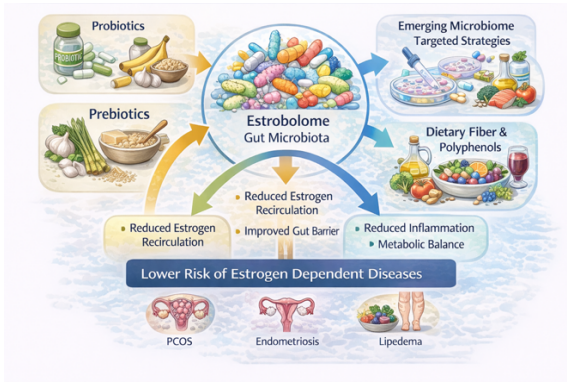
Examples of candidate microorganisms include species such as *Akkermansia muciniphila*, which has been associated with improved metabolic parameters and intestinal barrier integrity. Human proof of concept studies have demonstrated that supplementation with pasteurized *Akkermansia muciniphila* may improve metabolic markers in overweight individuals.

In addition to live microorganisms, increasing attention has been directed toward **postbiotics**, which refer to bioactive microbial products or metabolites capable of exerting beneficial effects without requiring viable organisms.

This strategy offers potential advantages in terms of stability, safety and regulatory standardization. By focusing on defined bioactive molecules derived from microbial metabolism, postbiotic approaches may allow more precise therapeutic interventions.

The transition from traditional probiotics toward microbiome based therapeutics represents an important step in the maturation of the field, bridging microbiology, biotechnology and clinical medicine.

Figure 3. Therapeutic strategies targeting the estrobolome and gut microbiota to modulate estrogen dependent diseases.




## CHAPTER 8: Translational Perspectives and Future Directions

The integration of microbiome science with endocrinology and immunometabolism opens new perspectives for translational research and clinical innovation. The concept of the estrobolome illustrates how microbial functions may influence hormonal homeostasis, inflammatory signaling and metabolic regulation.

Future advances will likely depend on the identification of functional biomarkers capable of characterizing microbiome activity rather than simply describing microbial composition. Enzymatic activity profiles, microbial metabolites and host inflammatory markers may provide more accurate insights into the functional state of the microbiome.

Precision microbiome approaches, integrating metagenomics, metabolomics and clinical phenotyping, may enable the development of personalized therapeutic strategies. Such strategies could include targeted probiotic interventions, dietary modulation, microbial metabolite supplementation or microbiota directed pharmacological therapies.

The development of standardized methodologies and well designed clinical trials will be essential to translate microbiome research into evidence based medical practice.

The convergence of microbiology, endocrinology, immunology and systems biology therefore represents one of the most promising frontiers in contemporary biomedical science.

## FINAL CONSIDERATIONS

The growing body of evidence linking the gut microbiota to estrogen metabolism highlights the relevance of the estrobolome as a functional component of systemic physiology. By influencing the enterohepatic circulation of estrogens, microbial communities may modulate hormonal exposure in multiple tissues.

This interaction gains particular importance in estrogen dependent diseases such as polycystic ovary syndrome, endometriosis and lipedema, conditions in which hormonal imbalance, chronic inflammation and metabolic dysregulation frequently coexist.

Although many mechanistic aspects remain under investigation, the integration of microbiome science with endocrine and metabolic research provides a valuable framework for understanding

complex diseases that involve multiple physiological systems.

As research progresses, microbiome based diagnostics and therapeutics may become important tools within precision medicine, contributing to more personalized and effective healthcare strategies.

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