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The Role of Uterine Microbiome Dysbiosis in Endometrial Cancer Development and Therapeutic Prospects

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Abstract: The uterine microbiome comprises diverse microorganisms essential for maintaining reproductive health by regulating immune responses, endocrine signaling, and cellular processes. Recent studies increasingly associate uterine microbiome dysbiosis—an imbalance in microbial composition—with the onset and progression of endometrial cancer (EC). Dysbiosis can trigger chronic inflammation, disrupt hormonal metabolism, and induce genetic mutations in endometrial cells, all contributing to carcinogenesis. Clinically, specific pathogenic microorganisms and reduced microbial diversity have been identified in EC patients compared to healthy controls, though findings remain inconsistent due to methodological variability and limited study sizes. Emerging evidence also suggests that microbial patterns might correlate with distinct EC subtypes, influencing disease aggressiveness and prognosis. Current therapeutic strategies aiming to restore microbial balance include probiotics, targeted antibiotic therapy, and experimental microbiome transplantation, each with unique potentials and challenges. Additionally, identifying early microbial biomarkers could facilitate earlier EC detection, enable monitoring of therapeutic efficacy, and predict patient prognosis. Despite these promising insights, significant gaps remain, particularly in establishing a clear causal relationship between microbiome dysbiosis and EC. Future research requires longitudinal human studies, advanced animal models, and interdisciplinary collaboration to validate microbial modulation as a viable therapeutic target. Addressing methodological limitations and standardizing microbiome analysis protocols will be crucial to harnessing the full potential of microbiome-based diagnostics and treatments, ultimately improving outcomes for patients with endometrial cancer.

1. Introduction

The uterine microbiome, comprising a diverse community of microorganisms that inhabit the uterine cavity, plays a crucial role in maintaining reproductive health. The balance of this microbial ecosystem is essential for the proper functioning of the endometrium, the innermost lining of the

uterus. The term "uterine microbiome" refers to the collective microbiota, including bacteria, fungi, viruses, and archaea, that exist in a delicate balance. This microbial community interacts with the host's immune system, endocrine signaling, and cellular processes to regulate uterine health. Disruptions to this balance, referred to as uterine microbiome dysbiosis, have been increasingly linked to various gynecological conditions, including endometrial cancer (EC), a malignancy arising from the endometrial lining of the uterus[1]. EC is one of the most common gynecological cancers worldwide, with incidence rates rising in recent decades, particularly among postmenopausal women. EC typically presents with abnormal vaginal bleeding, pelvic pain, and weight loss[2], and its pathogenesis is influenced by a variety of factors, including hormonal imbalances, genetic mutations, and inflammatory processes[3-5]. Recent evidence suggests that the uterine microbiome may also play a significant role in the development of EC, as alterations in microbial composition can potentially influence the molecular pathways associated with cancer initiation and progression.The mechanisms by which uterine microbiome dysbiosis contributes to the pathophysiology of EC are complex and multifactorial. Disruptions in the microbial community may lead to chronic inflammation, immune dysregulation, and altered hormone metabolism, all of which are known to contribute to carcinogenesis. In addition, microbial dysbiosis may affect the uterine tissue's susceptibility to DNA damage, promoting oncogenic mutations. Understanding these mechanisms is critical for developing novel therapeutic strategies and improving the prognosis of EC patients.

This review aims to explore the intricate relationship between uterine microbiome dysbiosis and the occurrence of endometrial cancer. We will examine the potential mechanisms through which microbial imbalance may influence EC development, discuss the clinical evidence linking microbiome alterations to EC, and explore the therapeutic implications of microbiome modulation in improving the prognosis of EC. By providing a comprehensive overview of these emerging insights, this review will contribute to a deeper understanding of the role of the uterine microbiome in endometrial cancer and highlight potential avenues for future research and clinical intervention.

2. Microbial Dysbiosis in Endometrial Cancer: Hormonal, Genetic, and Microenvironmental Mechanisms

2.1 Potential Mechanisms of Uterine Microbiome Dysbiosis in Endometrial Cancer Development

Uterine microbiome dysbiosis, or the imbalance in the microbial community within the uterine cavity, has been increasingly implicated in the development of chronic inflammation, a key driver of carcinogenesis[6]. Normally, a balanced microbiome helps regulate immune responses, maintaining immune homeostasis[7]. However, when dysbiosis occurs, the overgrowth of pathogenic microorganisms or the reduction of beneficial microbes can lead to an altered immune response. This can result in persistent low-grade inflammation, which is one of the hallmarks of cancer development.

In the context of EC, dysbiosis may activate local immune cells, such as macrophages and dendritic cells, which produce pro-inflammatory cytokines, chemokines, and other immune modulators[8]. This inflammatory environment can contribute to tissue damage, increased cellular turnover, and the accumulation of genetic mutations—all of which create favorable conditions for tumorigenesis. Additionally, chronic inflammation may enhance angiogenesis[9], the formation of new blood vessels that supply tumors with nutrients, thereby supporting tumor growth and metastasis.

Moreover, microbial metabolites, such as short-chain fatty acids (SCFAs) produced by beneficial bacteria, can modulate the activity of immune cells, either promoting or inhibiting inflammatory

pathways[10]. The dysregulation of these immune modulators due to microbiome imbalance could exacerbate the inflammatory processes that drive EC progression.

2.2 Impact on Hormonal Metabolism: Microbiome's Role in Endocrine Disruption and Potential for Endometrial Hyperplasia and Carcinogenesis

The uterine microbiome also influences the local metabolism of hormones, particularly estrogen, a key regulator of endometrial function[11]. Estrogen plays a central role in the normal growth and shedding of the endometrial lining during the menstrual cycle. However, when the microbiome is dysregulated, it may interfere with the metabolism of estrogen, potentially leading to an excessive accumulation of this hormone in the uterine cavity.

One significant mechanism by which microbiome dysbiosis can alter estrogen metabolism is through the disruption of the estrogen–gut microbiome axis[12]. Certain gut microbiota, particularly those producing beta-glucuronidase, can deconjugate estrogen metabolites in the liver, leading to higher concentrations of bioactive estrogen in the body[13]. When the uterine microbiome is dysbiotic, it may amplify this effect by enhancing the local reactivation of estrogen metabolites, leading to overstimulation of estrogen receptors on endometrial cells. This prolonged estrogen exposure can induce endometrial hyperplasia, a condition where the endometrium becomes excessively thickened, and is a known precursor to endometrial cancer.

Furthermore, dysbiosis may alter the expression of enzymes involved in steroidogenesis within the uterine tissue, thus influencing the synthesis and regulation of sex hormones like estrogen and progesterone[14]. These hormonal imbalances can promote the growth of abnormal endometrial cells, contributing to the initiation and progression of EC.

2.3 Cellular Signaling and Genetic Mutations: How Microbial Metabolites or Direct Microbial Action Can Alter Endometrial Cell Gene Expression

Microbial dysbiosis may also influence cancer development through direct interactions with endometrial cells, modulating cellular signaling pathways and promoting genetic mutations. Microbial metabolites, such as bacterial lipopolysaccharides (LPS), peptidoglycans, and other signaling molecules, can engage with receptors on epithelial cells lining the endometrium[15]. These interactions may trigger signaling pathways, including nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), that regulate inflammation, cell survival, and proliferation[16].

The activation of these pathways can lead to dysregulated cell division and survival, resulting in the accumulation of genetic mutations over time. Additionally, certain microbial species may directly affect DNA integrity by producing reactive oxygen species (ROS) and other genotoxic metabolites[17]. This can contribute to the genomic instability that is a hallmark of cancer cells, potentially initiating the process of carcinogenesis. Furthermore, changes in the microbiome can influence epigenetic modifications, such as DNA methylation and histone modification, which may alter the expression of tumor suppressor genes and oncogenes in the endometrium[18]. These epigenetic changes could enhance the proliferative capacity of endometrial cells, increasing the likelihood of malignant transformation.

2.4 Interaction Between the Microbiome and the Tumor Microenvironment

The interaction between the uterine microbiome and the tumor microenvironment (TME) is an area of growing interest in cancer research. The TME is a complex, dynamic environment composed of tumor cells, stromal cells, immune cells, and extracellular matrix components[19].

Microbiome-derived factors can directly influence the TME, shaping the conditions under which cancer develops and progresses. One of the primary ways the microbiome affects the TME is by modulating local oxidative stress levels. Dysbiosis, particularly an overgrowth of pathogenic bacteria, may increase the production of ROS, which can damage cellular components, including lipids, proteins, and DNA[20]. The accumulation of ROS within the TME can create a pro-carcinogenic environment, promoting cell damage, mutation, and tumorigenesis[21]. In addition, oxidative stress may contribute to immune evasion[22], as tumor cells can exploit oxidative damage to suppress the activity of immune cells that would otherwise target and eliminate malignant cells.

The microbiome can also influence the metabolic environment of the uterus. Certain microbial species can alter the local availability of nutrients, such as fatty acids, glucose, and amino acids, thereby affecting the metabolic pathways used by tumor cells[23]. This could potentially support the altered metabolism seen in cancer cells, such as the Warburg effect, where cells favor glycolysis even in the presence of oxygen. By altering the metabolic environment, the microbiome may facilitate tumor growth and survival, contributing to both primary tumor development and metastatic spread.

3. Clinical Evidence and Challenges: Linking Uterine Microbiome Dysbiosis to Endometrial Cancer Subtypes

3.1 Clinical Observations and the Association Between Uterine Microbiome Dysbiosis and Endometrial Cancer

Recent clinical research has begun to investigate the relationship between uterine microbiome dysbiosis and the onset of EC. While the field is still in its early stages, a growing body of evidence suggests that alterations in the uterine microbiome may play a critical role in EC pathogenesis. Several observational studies have explored the microbial composition of the uterine cavity in women with EC compared to healthy controls, with varying results. Scarf ò et al.[24] suggested that the development of endometrial carcinoma may be associated with estrogen dysregulation. Jiang et al[25]. proposed that it may be associated with immune dysregulation caused by gut microbiota imbalance.

In these studies, researchers have used advanced techniques, such as 16S ribosomal RNA sequencing and metagenomics, to identify microbial species present in the endometrial tissue or cervix[26]. Some studies have reported a significant difference in the microbial profiles of EC patients, with a higher prevalence of pathogenic bacteria, such as Gardnerella vaginalis, Prevotella spp., and Escherichia coli, compared to non-cancerous controls. Other studies have focused on the diversity and abundance of microbial species, showing that EC patients tend to have a reduced microbial diversity, which is often associated with dysbiosis. However, these clinical observations have not been entirely consistent, with some studies failing to find a clear association between uterine microbiome composition and EC[27]. This inconsistency could be attributed to various factors, including differences in sample collection methods, patient demographics, and study designs. Despite these challenges, the overall trend in the literature suggests that microbiome dysbiosis is indeed associated with an increased risk of EC and may contribute to its development.

3.2 Association Between Uterine Microbiome Changes and Cancer Subtypes

In addition to the overall association between microbiome dysbiosis and EC, some studies have begun to explore whether specific microbial alterations are linked to different subtypes of EC. Endometrial cancer is a heterogeneous disease, with different histological subtypes, including

endometrioid carcinoma, Which is the most common subtype, and non-endometrioid carcinomas such as serous carcinoma and clear cell carcinoma. Each of these subtypes has distinct molecular features, patterns of progression, and clinical outcomes.

Recent research has suggested that certain microbial profiles may be more closely associated with specific subtypes of EC. For example, studies have indicated that endometrioid carcinoma may be associated with higher levels of Lactobacillus spp.[28], which are typically considered beneficial microorganisms in the female reproductive tract. On the other hand, serous carcinomas, which tend to be more aggressive and have poorer prognoses, may be linked to an overrepresentation of pathogenic bacteria, such as Escherichia coli and Enterococcus spp[29]. These findings suggest that microbial dysbiosis might influence not only the development of EC but also the specific type and aggressiveness of the cancer. Further research is needed to clarify these associations and determine whether specific microbial signatures can serve as diagnostic or prognostic biomarkers for EC subtypes[30]. Identifying such microbial patterns could lead to more targeted interventions and personalized treatment strategies for patients with EC.

3.3 Challenges and Limitations in Clinical Observations

Despite the growing interest in the relationship between uterine microbiome dysbiosis and EC, several challenges remain in clinical research, limiting the ability to draw definitive conclusions. One major limitation is the relatively small sample sizes in most studies, which can reduce the statistical power of the findings. The heterogeneity of EC patients, including differences in age, menopausal status, comorbidities, and prior medical treatments, further complicates the interpretation of results. Additionally, the uterine microbiome is influenced by multiple factors, including hormonal fluctuations, sexual activity, and antibiotic use[31], all of which may introduce confounding variables that are difficult to control in clinical studies.

Another critical challenge lies in the methodologies used to assess the uterine microbiome. While high-throughput sequencing technologies, such as 16S ribosomal RNA (rRNA) sequencing and metagenomic analysis, have provided valuable insights into microbial composition, they also have inherent limitations. These techniques primarily identify bacterial species, often overlooking the potential roles of fungi, viruses, and archaea in the uterine microenvironment. Furthermore, variations in sample collection methods—ranging from cervical swabs to endometrial biopsies—introduce inconsistencies in microbial profiles, as different sampling techniques may yield distinct microbial compositions. Contamination during sample collection and processing also poses a significant challenge, potentially distorting findings and leading to unreliable conclusions. In addition to technical limitations, variability in study design has led to inconsistencies in reported results. Differences in patient selection criteria, sequencing protocols, and bioinformatics pipelines contribute to discrepancies across studies, making it difficult to compare findings and establish a unified understanding of how microbiome alterations influence EC. Moreover, most existing studies are observational in nature, which restricts the ability to establish causality between microbiome dysbiosis and EC. It remains unclear whether microbial alterations directly contribute to carcinogenesis or if they are secondary changes occurring as a result of the disease. Longitudinal studies and interventional trials are needed to clarify the temporal relationship between microbiome dysbiosis and EC onset, as well as to explore the potential for microbiome-based diagnostics and therapeutics.

Despite these challenges, research into the uterine microbiome's role in EC continues to advance, driven by the potential for novel biomarkers and therapeutic targets. Future studies with larger sample sizes, standardized methodologies, and mechanistic investigations will be crucial to overcoming these limitations and elucidating the complex interplay between microbial dysbiosis

and endometrial carcinogenesis.

4. Targeting the Uterine Microbiome: Therapeutic Interventions and Diagnostic Biomarkers in Endometrial Cancer

4.1 Strategies for Modulating the Uterine Microbiome

As emerging evidence suggests a significant link between uterine microbiome dysbiosis and EC, targeting the microbiome offers a promising therapeutic approach to improve prognosis and possibly reduce cancer incidence[32]. Several strategies are being explored to restore a healthy microbial balance within the uterine environment, thereby potentially reducing the risk of cancer progression. Probiotic therapy, which involves the administration of live beneficial microorganisms, is one potential strategy for restoring a balanced uterine microbiome[33]. The use of probiotics to maintain or restore the normal microbial composition of the uterus has garnered attention due to their ability to inhibit pathogenic bacteria and promote the growth of beneficial microbes such as Lactobacillus spp. These beneficial bacteria are thought to help maintain an acidic vaginal pH, preventing the overgrowth of harmful microorganisms that can contribute to inflammation and carcinogenesis.

While the use of probiotics in the vaginal microbiome is well-established, studies specifically targeting the uterine microbiome in the context of EC are still in the early stages. However, preliminary data suggest that probiotics may not only improve microbial diversity but also modulate the local immune response, reducing chronic inflammation and potentially lowering the risk of EC development[34]. Further research is needed to identify the most effective probiotic strains and determine optimal dosing and administration methods for achieving therapeutic outcomes in the uterine microbiome. Another potential intervention is the use of antibiotics to target and reduce the abundance of harmful microorganisms within the uterine cavity[35]. In cases where pathogenic bacteria, such as Gardnerella vaginalis, Escherichia coli, or Prevotella spp., are implicated in dysbiosis and EC development, antibiotic therapy may help restore microbial balance by eliminating or reducing these pathogens. This approach has been widely used in treating other gynecological infections, such as bacterial vaginosis, and could be extended to address microbial imbalances that contribute to EC. However, the use of antibiotics is not without its challenges. Overuse or inappropriate use of antibiotics can lead to antibiotic resistance, further exacerbating dysbiosis and contributing to long-term health risks. Additionally, antibiotics can disrupt the overall diversity of the microbiome, potentially leading to unintended side effects, including the overgrowth of opportunistic pathogens[36]. Therefore, careful consideration and targeted antibiotic therapy, based on microbial profiling, will be necessary to optimize outcomes without causing adverse effects. Another innovative strategy is microbiome transplantation, which involves transferring healthy microbial communities from a donor to a patient[37]. Although primarily used in the context of gut microbiome transplantation, recent studies have suggested the potential for vaginal or uterine microbiome transplantation to restore microbial balance in patients with dysbiosis. The concept is that by reintroducing a healthy, diverse microbial community, it may be possible to correct the imbalance and reduce the risk of EC development.

While microbiome transplantation holds significant promise, its application in the uterine environment is still experimental. Research is needed to determine the feasibility, safety, and effectiveness of this approach, as well as the best methods for microbial selection and transplantation. Furthermore, long-term outcomes and potential risks of introducing foreign microbial communities into the uterus must be thoroughly evaluated before widespread clinical implementation.

4.2 The Need for Early Diagnostic Biomarkers of Uterine Microbiome Dysbiosis

In addition to therapeutic strategies for microbiome modulation, the identification of early biomarkers for uterine microbiome dysbiosis is critical. Such biomarkers would not only enable earlier detection of EC but could also serve as indicators of therapeutic response and recovery. By identifying specific microbial signatures or metabolites associated with dysbiosis[38], clinicians could potentially detect precancerous changes or early-stage cancer before clinical symptoms manifest. This could lead to earlier intervention and better patient outcomes.

Furthermore, the presence or absence of these biomarkers could provide valuable insights into treatment efficacy. If a therapeutic intervention, such as probiotic therapy or antibiotic treatment, successfully restores microbial balance, the disappearance of these biomarkers could serve as a signal that the treatment has effectively addressed the dysbiosis and possibly reversed the progression toward cancer. Conversely, persistent microbial dysbiosis despite intervention might indicate that further therapeutic adjustments are necessary. Biomarkers linked to microbial dysbiosis could also serve as non-invasive indicators of EC prognosis[39]. For example, the detection of specific pathogenic bacteria or microbial metabolites in vaginal swabs or endometrial biopsies might help predict cancer recurrence, metastasis, or resistance to conventional therapies. Such biomarkers would not only improve diagnostic accuracy but also allow for personalized treatment plans tailored to the unique microbial composition of each patient.

In conclusion, modulating the uterine microbiome through various therapeutic strategies holds significant promise in improving the prognosis of EC patients. Whether through probiotic therapy, antibiotic treatment, or microbiome transplantation, restoring microbial balance may help mitigate the risk of cancer development and recurrence. Furthermore, the identification of early biomarkers associated with dysbiosis could lead to earlier detection and more effective treatment strategies, ultimately improving patient outcomes. As research in this area continues to evolve, it may pave the way for microbiome-based interventions that could complement existing therapeutic modalities and redefine the management of EC.

5. Discussion

One of the most pressing challenges in this field is the lack of clarity regarding the causal relationship between microbiome dysbiosis and the development of EC. While observational studies consistently suggest an association between microbial imbalances and EC, it remains unclear whether these microbiome alterations are a cause or a consequence of the disease. The cross-sectional nature of most studies makes it difficult to establish a temporal relationship. Therefore, large-scale longitudinal studies are needed to determine whether dysbiosis precedes cancer development or if it occurs as a result of the inflammatory and tumorigenic processes in the endometrium. Additionally, animal models that more closely mimic the human uterine environment would be invaluable in exploring the mechanistic pathways by which microbial imbalances may directly contribute to carcinogenesis[40].

The existing literature on uterine microbiome dysbiosis and EC has several limitations that restrict its ability to provide definitive answers. Many studies are hampered by small sample sizes, which reduce the statistical power and generalizability of their findings. The variability in methodologies across studies—such as differences in microbial sampling techniques, sequencing methods, and bioinformatics analysis—makes it challenging to compare results and draw consistent conclusions. Furthermore, the complexity of the uterine microbiome itself, which is influenced by various factors including hormonal fluctuations, sexual activity, and previous infections, adds another layer of difficulty in interpreting results.

Another limitation is the focus on bacterial microbiota, while other microbial communities,

including fungi, viruses, and archaea, have largely been neglected in most studies. Since these non-bacterial microorganisms may also play a role in the uterine microenvironment, their inclusion in future studies could provide a more comprehensive understanding of the microbiome's impact on EC.

In terms of clinical translation, several obstacles prevent the widespread application of microbiome-based therapies for EC. One of the primary challenges is the lack of standardized methodologies for microbiome profiling. Variations in sample collection, DNA extraction methods, and sequencing technologies can lead to inconsistent results, making it difficult to establish robust diagnostic or therapeutic biomarkers for EC. Additionally, assessing the therapeutic efficacy of microbiome interventions, such as probiotics, antibiotics, or microbiome transplantation—remains a significant hurdle. Clinical trials with rigorous design are needed to evaluate the safety, effectiveness, and long-term outcomes of these interventions in patients with EC.

Another challenge lies in the implementation of personalized medicine based on microbiome analysis. Although microbial profiling holds promise for identifying patient-specific therapeutic strategies, the current understanding of how specific microbial alterations influence cancer progression is still incomplete. Therefore, further research is required to determine how best to tailor microbiome-based treatments to individual patients and how to monitor treatment success in a reliable and reproducible manner.

6. Conclusion

In conclusion, the relationship between uterine microbiome dysbiosis and EC is an emerging area of research that offers exciting potential for improving cancer prevention, diagnosis, and treatment. While current studies suggest that microbial imbalances may contribute to the development and progression of EC through mechanisms such as immune system activation, hormonal modulation, and alterations in the tumor microenvironment, the precise mechanisms remain unclear. Further research is needed to confirm causality and to explore the broader roles of non-bacterial microorganisms, such as fungi and viruses, in EC pathogenesis. The potential for microbiome-based interventions, such as probiotics, antibiotics, or microbiome transplantation, represents a novel approach to EC therapy. However, clinical translation is hampered by limitations in current research methodologies, a lack of standardized protocols, and challenges in evaluating the efficacy of microbiome-based therapies in diverse patient populations. Future studies, particularly large-scale longitudinal studies and animal models, are crucial to advancing our understanding of how microbiome dysbiosis contributes to EC and to the development of effective treatment strategies. Finally, the success of microbiome-based therapies in EC will depend on the collaboration of experts across multiple disciplines, including microbiology, immunology, oncology, and bioinformatics. Only through interdisciplinary research can we unlock the full potential of the uterine microbiome as a target for cancer prevention and treatment, ultimately improving outcomes for patients with endometrial cancer (Figure 1).

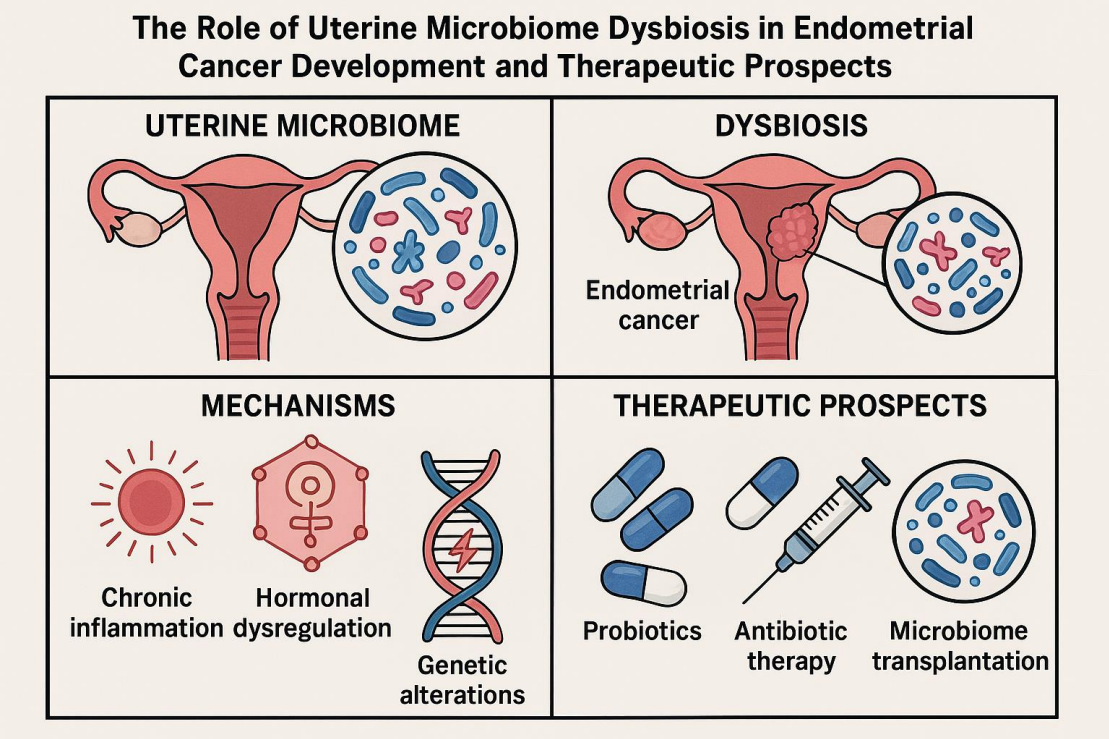

Figure 1: The association between endometrial cancer and endometrial microbiota

Declaration of competing interest

The authors declare no Conflicts of Interest for this article.

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