

Probiotics in Women and Pediatrics Health: A Narrative Review

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ABSTRACT

Probiotic use to improve health is not new; but recently, it has attracted much attention concerning human health and diseases. The human gut is a delicate ecosystem where bacteria and host cells interact with each other. This is an important part of gut homeostasis and human development. Disruption of this sensitive ecosystem may have detrimental health repercussions linked to impaired gut microbiota (GM). GM were extensively examined as an underlying mechanism for disease development and progression. Additionally, it was used as a tailored method for preventing and treating disease. Because of the strong association between GM, health, and disease, there has been much interest in employing probiotics or living microorganisms, to regulate GM to prevent or cure specific diseases. Herein, probiotics' role in enhancing women's and pediatric well-being was addressed as a marker of disease and as therapeutic avenues; where we discussed probiotics indications, efficacy, safety profiles, and future prospects in clinical practice.

Keywords: Probiotics; Women; Pediatrics; Health; Biomarker.

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INTRODUCTION

Our bodies are diversely inhabited by microorganisms and endure constant changes. The appropriate composition of these microbiotas is crucial for the human body's correct function [1]. A microbiota is comprised of all microorganisms [bacteria, virus, fungi, and protozoa] that colonize the skin, respiratory tract, genital system, and particularly the gastrointestinal tract [2].

Gut microbiota (GM) coordinates and stimulates the immune system and maintains homeostasis in the body. They participate in the manufacture of numerous essential vitamins for the host, including vitamins K and B vitamins. GM metabolizes undigested meal remnants, from which more energy is derived. A balanced relationship between bacterial strains and our bodies enables homeostasis [3]. The diversity of natural flora varies with age, health, living situations, and the use of antibacterial, disinfectants, and certain cosmetics. A

lot of research has been done to define what "healthy" GM is and how it affects the way the body works, but there is no current consensus regarding the definition of healthy GM. In times of health, the GM is stable, resilient, and works in symbiosis with the body. A healthy GM community usually has a lot of different kinds of organisms, a lot of different kinds of microbes, and a stable core microbe [4].

But it is important to remember that the relative distribution of microorganisms is different for each person and can even change within the same person. Furthermore, there are obvious anatomical differences between males and females, as well as reports of differences in the composition of their GM [5].

Some research suggests that commensal microbiota can influence and alter sex hormone levels; this effect appears to be bidirectional. Gut microbes have been linked to various disorders, which support the hypothesis that a balanced GM population is good for mental and metabolic health. As a result, women need to maintain a healthy lifestyle and dietary habits to keep GM balanced [6].

The newborn's colonization with GM begins immediately after birth, depending on the mode of delivery. Whether vagi-

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nal birth or Caesarian section. A balanced diet during puberty prepares the GM to function appropriately in adult life [7].

Pediatric GM differs greatly from adult GM; there are compositional and functional qualities that differ from those of healthy adults. Furthermore, GM differs from one child to another in the pediatric age group [8]. In addition to the mode of delivery, other factors that may affect the composition of GM include host genetic variation, type of newborn feeding, age, diet, lifestyle, diseases, and medications [9].

A probiotic is a microbial substance capable of stimulating the growth of another microorganism. They were first described in 1965 by Lilly and Stillwell [1, 9, 10]. Their definition was changed to "a living microorganism that benefits the host by altering GM equilibrium". When taken in adequate amounts, probiotics contribute to a beneficial effect on the host. A growing body of evidence suggests that probiotics may be beneficial in a variety of illnesses [10].

The most frequently used probiotic bacteria belong to the lactic acid-producing genera *Lactobacillus* or *Bifidobacterium*, and some non-bacterial yeast strains of *Saccharomyces* are also used. Despite abundant and readily available evidence demonstrating the advantages of probiotic use, medical professionals remained hesitant to suggest probiotics to patients; this may have been due in part to their moderate knowledge about probiotics and attitudes toward them as a result of a number of safety concerns. Herein we will discuss the role of probiotics in women and pediatric age group diseases and their potential role in diagnosing and treating related diseases [11, 12].

PROBIOTICS AND WOMEN'S HEALTH

Probiotics are crucial in maintaining a healthy GM, which is essential for overall female wellness. Earlier studies have shown that probiotics can improve digestion, enhance immunity, and reduce inflammatory responses [1–3]. Moreover, probiotics help treat a range of ailments, including diarrhea and urinary tract infections. In addition to improving skin health by fostering a healthy microbiota, hence decreasing acne [2].

Regarding women's health, probiotics help prevent bacterial or yeast vaginal infections since they restore the balance of vaginal microorganisms [5, 12]. Probiotics were utilized in the field of obstetrics. It was found to lessen the incidence of premature labor and preeclampsia during pregnancy [5, 13]. Probiotic administration was suggested for therapeutic potential in women's disease; the introduction of certain bacteria species aimed to correct a deficiency or trigger an overgrowth was considered to be of therapeutic value [10]. Incorporating including probiotics in one's daily diet or consuming probiotic supplements can have numerous health benefits, especially for woman health. Herein we will discuss probiotics' role in women's disease and malignancies.

PROBIOTICS AND INFECTIONS

Probiotics are widely employed as a treatment for bacterial vaginosis (BV), a common illness characterized by an abnormal bacterial balance in the vagina. Probiotics can restore the harmony of bacteria and reduce symptoms of BV, like vaginal discharge, itching, and soreness. Furthermore, it helps prevent BV recurrence by keeping the vaginal environment healthy in a systematic review by van de Wijgert et al., probiotics were recommended as a promising therapeutic and preventive option for BV. [13].

Probiotic dose and duration of therapy in BV vary based on women's risk factors and the probiotic strain used. Probiotic doses range from 1–10 billion colony-forming units (CFUs) per day for about two months. *Lactobacillus acidophilus* and *Lactobacillus rhamnosus* are two of the most common strains. Once taken as directed, probiotics are usually safe. But taking higher doses may cause side effects like bloating and gas. There were rare reports of allergies to probiotic use and some reported infections, especially among people with depressed immunity. Interaction with medications was also reported, particularly with anti-infective drugs [14].

Probiotics have been investigated as a potential treatment for vulvovaginal candidiasis (VVC), the second most prevalent infection in reproductive-age females, which presents as pruritus, discomfort, irritation, dyspareunia, dysuria, and a curd-like discharge [15]. VVC has been linked to a statistically significant increase in the likelihood of spontaneous miscarriage, a higher risk of premature membrane rupture, preterm birth, chorioamnionitis, and neonatal cutaneous candidiasis [15, 16].

Some researchers have declared the beneficial role of probiotic usage in VVC; further work is required to corroborate these findings. The most often used probiotic strains for treating VVC are the same as for BV; the suggested dose is 1–2 capsules per day each capsule has 1–10 billion CFUs, given orally or by vaginal application; it should be emphasized that it should not be used in exchange for established therapy for fungal infections [17].

Pregnancies with COVID-19 suffer increased mortality and a more aggressive disease course [18]. Researchers discovered a significant shift in vaginal microorganisms (VM) among seropositive moms. The more severe the disease, the more disturbed VM becomes. This suggests the possible use of these modifications as a risk assessment tool for preterm labor in COVID-19 mothers and a treatment pathway via the modified VM [19]. GM's role in resolving COVID-19 in females is still under investigation. Nevertheless, research indicates that GM plays a significant function in the immune system and can reduce the severity of COVID-19 manifestations. Women with greater gut microbe diversity have a more robust immunological response to COVID-19, lowering the intensity of symptoms. Furthermore, specific probiotics were able to reduce the inflammatory response and increase general wellness, thereby assisting women in their recovery. Further research is needed to confirm whether GM can cure and prevent COVID-19 in women [19, 20].

PROBIOTICS IN POLYCYSTIC OVARIAN DISEASE (PCOS) AND INFERTILITY TREATMENT

PCOS is a common endocrinopathy with insulin resistance as the main underlying pathology. Patients suffered from obesity, irregular cycles, and hyperandrogenism. According to studies, PCOS patients have lower GM diversity than healthy women [21–23].

The Ostadmohammadi et al. study found that probiotics can help reduce the symptoms of PCOS, such as hirsutism, acne, and obesity; moreover, they can improve insulin sensitivity, reduce inflammation, and enhance reproductive hormone levels and fertility in PCOS women. These findings imply that probiotics may be useful for managing PCOS symptoms and improving overall health. For sub-fertile couples undergoing, an alteration in vaginal and seminal fluid microbes

was correlated with unsuccessful outcomes [22]. Actually, the detection of *Lactobacillus* in women's lower and upper genital tract favors good outcomes (Odds ratio 0.66) in terms of pregnancy and live birth [24]. Profiling of vaginal microbes accurately predicted positive in-vitro fertilization (IVF) with a prediction accuracy of 94 percent [25].

Probiotics supplementation does improve pregnancy rates IVF cases; through multiple pathways [26] (Figure1). Together, these effects will contribute to higher embryo implantation and conception rates. The beneficial effect of probiotics extends beyond GM, as they reduce stress levels among the infertile couple. Stress is an important cofounder that inversely impacts fertility by interfering with the circadian hormonal pattern and decreasing blood supply to the reproductive system [27].

PROBIOTICS IN MALIGNANCIES

Probiotics in cervical cancer

There is an important link between the intake of more probiotics and slowing the spread of cervical cancer, but the exact mechanism is unknown [28].

Some have attributed it to a direct probiotic effect by enhancing local cervical immunity and lessening inflammation, a critical element in how cervical cancer starts and propagates. Or through a beneficial effect on vaginal lactobacilli, an indirect probiotic role. The latter is critical in the development of a newer version of the human papillomavirus vaccine, which is a major cause of cervical cancer [28, 29].

At least 10 billion CFUs should be taken every day for at least 13 weeks. It's important to remember that different probiotics may have different effects on how cervical cancer gets worse. Probiotics should be administrated in conjunction with other therapies like chemotherapy and radiation for the best results. Interestingly, probiotic benefits extend into the treatment time of cervical cancer patients; Qiu et al. showed that probiotic supplements reduced the incidence of radiation-induced diarrhea [30].

Probiotics and breast cancer

Diminished GM diversity was associated with malignant tumors, especially breast cancer which showed less diversity of GM. Other studies reported increased amounts of certain bacterial strains among breast cancer cases. Evidence suggests that certain bacteria may be implicated in the formation or progression of breast cancer, implying a preventative

role for genetic modification in breast cancer. More investigation is required to comprehend how this association operates and how it may be utilized to prevent or treat these ailments [31, 32].

PROBIOTICS IN MENOPAUSE

In menopausal women, oral administration of probiotics was used as an adjuvant therapy to estrogen withdrawal and was also used to improve cognitive function and mental illness in older patients [33, 34]. The most common dose used in studies is 10 billion CFUs taken orally each day for eight weeks. The primary benefit was to improve menopausal symptoms, such as hot flashes, night sweats, and a dry vagina. Reduced urinary tract infections and improved general digestive health are further secondary advantages [32].

Studies have shown that GM may help improve cognitive and mental health by controlling inflammatory and endocrine secretions, making neuroactive chemicals, and communicating with the vagus nerve. Inflammation is a key pathophysiological factor of mental diseases and a target for GM-based treatments, which requires a deeper understanding of the underlying processes [33].

Recent evidence has discussed a molecular link between GM and the immune system as a driver of the systemic proinflammatory state. These pathways correlate with the onset and progression of cardiovascular and metabolic diseases like diabetes and osteoporosis in postmenopausal women. The potential use of genetically modified organisms as biomarkers for certain metabolic diseases would allow for the implementation of preventative and effective treatment measures [35, 36].

Opportunities to improve women's health can be gained through GM modulation in the general population. Personalizing a dietary approach with the implementation of targeted probiotics seems promising.

PROBIOTICS USE IN OBSTETRICS

The value of using probiotics in gestational diabetes (GDM) was inconclusive. Lagowska meta-analysis [37] recommended their use as it reduced insulin levels, blood sugar, and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR); however, the probiotics beneficial effect was specific to the type of probiotic used. They showed that supplementation lowers serum glucose, insulin levels, and the HOMA-IR index, but only in pregnant women with GDM [37]. Another meta-analysis confirmed a reduced risk of GDM by 33% (risk ratio 0.68, 95% CI: 0.48, 0.95) by probiotic use [38].

Conversely, a randomized control trial found no benefit of probiotic use on fasting glucose levels in two groups of newly diagnosed GDM after six weeks of follow-up. Interestingly, a favorable effect was demonstrated on lipid levels. Probiotic use in GDM seems encouraging; further longitudinal studies are warranted to validate their use [39].

Probiotics' role in preeclampsia (PE) and other hypertensive diseases of pregnancy was also researched. Their use showed no meaningful effect on reducing the odds of PE; odds ratio = 1.57, (95% CI= 0.62 to 3.97, P = 0.35). The authors proposed scarcity and heterogeneity among the studies to be the cause [40].

Probiotic role in preventing and treating PE cases is currently under study; one option is a fecal microbiota transplant. The mechanism by which probiotics contribute to PE

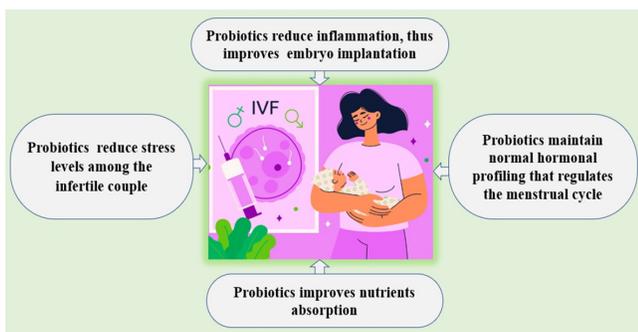


Figure 1. The mechanism by which probiotics improve in vitro fertilization (IVF) outcome.

cases [41] is explained in Figure 2. Still, there is little evidence to justify using them alone rather than an adjunctive benefit. Some recommended their use post-delivery to improve maternal wellness owing to probiotics' positive effect on reducing infection and depression symptom [41].

A growing body of research supports the use of GM in predicting and preventing preterm labor (PL). One study discussed a 50% reduction in PL risk by *Lactobacillus rhamnosus* supplementation in a case-control study [42].

Added to the probiotic potential preventive role, probiotics were examined in predicting PL. Reducing *Lactobacillus species* was linked to an increased risk of PL, which opens a potential therapeutic role by targeting vaginal microbes to prevent and treat PL [43, 44].

Overall, much research is warranted to determine the optimal dose, regimen, and specific strains of probiotics that are most beneficial in obstetrics, which will evolve our way of managing diseases.

PROBIOTICS IN PAEDIATRICS

Probiotics for children are available in a variety of forms, including dietary supplements, fermented products (yogurts), and nonfermented products (infant formulas) [45]. Probiotics are extensively administered to treat and/or prevent a variety of pediatric conditions [46].

Current evidence supports the use of probiotics in infant colic in breastfed infants and for preventing antibiotic-associated diarrhea (AAD) in the presence of risk factors such as the choice of an antibiotic agent, duration of treatment, the patient's age, comorbidities, need for hospitalization, or previous episodes of AAD. There is no evidence that a specific strain may be beneficial in the management of Crohn's disease and irritable bowel syndrome [47]; conversely, probiotics were significantly beneficial in reducing rates of rotavirus diarrhea. Recent studies did not show sufficient evidence to support the use of probiotics in preventing or treating acute gastroenteritis, *Clostridium Difficile*-Associated Diarrhea (CDAD), functional constipation, regurgitation, ulcerative colitis, eradication of *H. pylori*, and necrotizing enterocolitis [48].

Probiotics were part of several guidelines for the management of different pediatric conditions; for example, European guidelines currently recommend the use of probiotics in the treatment of acute gastroenteritis [49]. There was a dilemma regarding probiotics use in preterm, especially among those with very low birth weight. Previous literature listed prematurity as a contraindication to using probiotics. Extensive

work recently revealed favorable results in terms of decreasing the risk of late-onset sepsis, mortality, and severe necrotizing enterocolitis [50]. In addition, decreased enteral feeding duration positively affects weight gain [51]. All these factors make its use in preterm labor very promising; however, the specific type to be used, the regimen, and the duration of therapy, together with other fundamental factors, have yet to be determined [52].

GM is a crucial regulator of a bidirectional conversation between the gut and the brain (gut-brain axis). GM is referred to as a supplementary regulator of this axis. Changes in GM composition were associated with a number of neuropsychiatric disorders and neurodegenerative illnesses, including autism and attention deficit hyperactivity disorder in children. The investigation of this axis' regulation may lead to methods for improving mental health and treating psychiatric diseases by changing GM [53, 54].

The majority of what we know comes from studies on animals, but the use of prebiotics has led to some encouraging results. It has been shown that GM can change how genes are expressed in the host by affecting epigenetic processes, a very dynamic and potentially reversible process. The fact that epigenetic changes associated with ageing can be reversed opens up new avenues for treating diseases associated with ageing [55].

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most prevalent neurodevelopmental diseases of childhood that is often diagnosed throughout childhood and lasts into adulthood. Affected kids struggle with managing impulsive activities, paying attention, and being excessively active. ADHD was linked to many perinatal risk factors, such as mode of delivery, gestational age, type of feeding, maternal health, and early life stressful events. All of these risk factors were correlated with changes in GM. Dietary elements that alter GM may influence the onset or the symptoms of ADHD [56]. Autism, often known as an autism spectrum disorder (ASD), is a neurodevelopmental disorder marked by atypical social skills, communication, and behaviors. Children with autism showed an increase in GM diversity. In fact, an abundance of *Bacteroidetes* has been linked to severe autism [57]. The aforementioned observation prompted Kang et al. to conduct a therapeutic trial in which they transplanted fecal microbes from healthy children to those with autism, which proved effective in lowering behavioral autism spectrum disorder scores and improving gastrointestinal function [58].

Evidence for the effectiveness of probiotics in pediatric illnesses is conflicting due to methodological inconsistencies, different GM strains, varied doses, and a lack of sufficient sample size. More meticulously designed research is required to determine the beneficial GM strains employed and to clarify safety concerns [59, 60].

CONCLUSION

The GM is a dynamic, complicated system, and it can be challenging to correctly assess and interpret changes in it. GM is currently being used as a biomarker for disease progression and prediction. Promising therapeutic approaches were demonstrated by modifying GM with probiotics, particularly in mental health, metabolic disorders, and cervical cancer prevention. The use of probiotics is hindered by several issues; for instance, the effect of GM modification on human well-being reveals individual variance. Hence, we cannot determine the cause-and-effect relationship between probiotic

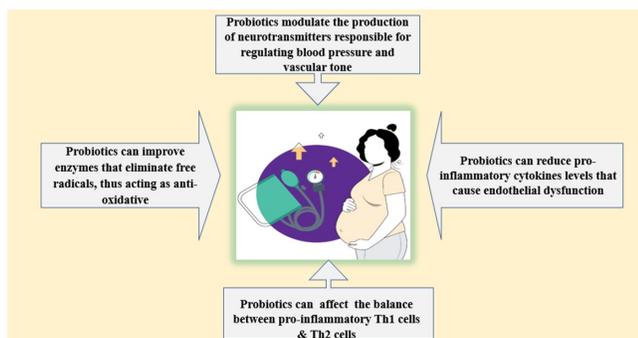


Figure 2. The main pathways that probiotics convey their beneficial effect in preeclampsia.

usage and enhanced health, which limits their global use. Little is known about how environmental factors affect GM in women and children, particularly in highly polluted settings. There is a lack of information regarding the long-term effects of changing GM in women and children, not to mention the moral aspects of modifying GM since it may have unanticipated health consequences. To broaden the use of probiotics, further study is required to prove their safety, effectiveness, and dosage.

ETHICAL DECLARATIONS

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Ethics Approval and Consent to Participate

Not required.

Consent for Publication

None.

Availability of Data and Material

None.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

Nori W, Akram NN, and Al-kaabi MM designed the research, wrote the paper, and analyzed the data. Nori W did the literature review, revised it, and drafted the manuscript. All authors have read and agreed on the final version of the manuscript.

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