Chapter 08

Microbial Matrimony: Exploring the Potential of Prebiotics and Probiotics for Optimal Reproductive Health

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ABSTRACT

The symbiotic relationship between the microbiome and reproductive health is among the most discussed topics of the last decade. Live microorganisms, probiotics with multiple physiological functions, are considered alternative therapeutic agents in improving reproductive ability. It has been evidenced that there is a great diversity of microbes in the reproductive systems of both sexes, suggesting the gut microbiome is a factor in maintaining reproductive health. Dysbiosis of the reproductive microbiome is linked with various reproductive disorders and adverse pregnancy outcomes, indicating that probiotic therapy may be an option for microbiome balance restoration and reproductive function mitigation. Probiotics work by adjusting the bacterial population and the microbiota's activity, regulating the host's metabolism and immune response. Prebiotics, which are non-living substrates that preferentially support the development of beneficial microbes, are a complementary method of promoting reproductive health by promoting the growth of probiotic strains. This chapter explores the potential of prebiotics and probiotics to be utilized as novel therapeutic modalities to improve reproductive health, emphasizing their clinical applications and future research and practice trends.

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INTRODUCTION

Probiotics are live microbes with an extensive variety of the effects they have on their hosts. The food, especially fermented products such as yogurt, makes the majority of the commercial probiotics. Probiotics have several health benefits that can be categorized into four key domains: reduction of pathogen growth (Yan et al., 2007), enhancement of intestinal barrier function (Yan et al., 2011), regulation of the immune system (La Fata et al., 2018), and control of pain perception (Rousseaux et al., 2007). Thus, use of probiotics may be helpful therapeutically when treating the vastness of diseases. It has been comprehensively recognized that there exists a diverse microbiome in the animal system and that it plays the role of maintaining a normal physiology and favorable health of an organism (Dominguez-Bello et al., 2019). Scientific research has also focused on the discovery of microbes in the reproductive organs of both male and female sexes. The reproductive microbiota were primarily detected in semen from males (Lundy et al., 2021), whereas microbiomes were found everywhere in the reproductive tract from females (Heil et al., 2019), and each part or tissue of the reproductive system was colonized by a distinctive microbiome with a particular composition. With commensal microorganisms, the ecosystem is balanced in the reproductive process, thereby, increasing host fertility and performance (Rowe et al., 2020).

Dysbiosis of the microbiota of the reproductive tract may promote various diseases, aberrant pregnancy outcomes, and embodiment in the female reproductive system (Schoenmakers et al., 2019). Furthermore, numerous studies have demonstrated that gut microbiota also plays an important role in the regulation of some relatable diseases and preservation of the reproductive system basal state of health (Quaranta et al., 2019). Probiotic treatments, which address the microbiome, are becoming another logical alternative treatment modality when conclusive evidence reveals that the microbiome is linked to reproductive health and related conditions. Lots of recent researches have established a probiotic-based medicine or supplements prevent related diseases and reproductive disorders (Helli et al., 2022). Given the correlation between metabolic health and reproductive function, probiotics may enhance host reproductive function by controlling host metabolism (Palmer et al., 2012). Probiotics can affect the various membrane structures associated with reproduction. They also support epithelial barrier function and membrane integrity, which are necessary for successful blastulation and the development of the amnion, chorion, and placenta (Reid et al., 2013). Additionally, numerous studies have demonstrated the immunomodulatory effect of probiotics, and because some probiotics can disrupt the inflammatory cascade, they may be beneficial in certain reproductive functions and diseases related to them (Sanz, 2011).

On the other hand, prebiotics are described as "non-viable substrates that act as nutrients for beneficial microbes possessed by the host, such as administered probiotic strains and indigenous (resident) microorganisms" (Gibson et al., 2017) by the International Scientific Association for Probiotics and Prebiotics (ISAPP). This is a su bstance that the human body cannot break down, as it is resistant to gastric acid and is not broken down by enzymes found in mammals or consumed by the gastrointestinal system. The intestinal flora digests prebiotics and specifically activates some of the colon's bacteria, changing their development and activity in the host's favor (Gibson and Roberfroid, 1995). According to another study prebiotics are substances that can be deliberately fermented to change the structure and activity of the gut's beneficial host health flora, often known as "bifidogenic factors." (Gibson et al., 2004). Prebiotics were redefined in 2016 by the International Scientific Association for Probiotics and Prebiotics as compounds that the host intestinal flora may utilize and alter selectively, expecting to improve host health. The term "prebiotics" has been redefined to encompass non-carbohydrates, and its mode of action is no longer restricted to the gastrointestinal system or food (Gibson et al., 2017).

Typically, they are plant-based products like polysaccharides (FOS, GOS, fructose- or galactooligosaccharides, inulin) or non-sugar molecules that are fermented by the microbiota instead of being broken down by the host's enzymes and enhance the host's health. Another critical source of prebiotics in the human diet may be dairy products, most notably yogurt. The following substances have prebiotic qualities: Lactose, phosphates, oligosaccharides, especially those that contain N-acetylglucosamine, lactoperoxidase enzymes, nucleotides, lysozyme enzymes and alfa-lactoalbumin, glycomacropeptide (GMP) and lactoferrin (Vega-Bautista et al., 2019). This chapter will profile the prebiotic and probiotic novel therapeutic modalities that can play a pivotal role in improving reproductive health. It will focus on their clinical applications and future trend specialization for research and practice.

Diversity of Probiotics and Prebiotics

Probiotics

Probiotics are a diverse group of organisms with a broad distribution range that can be classified into three main categories: *Lactobacilli, Bifidobacteria,* and some others. Considering the fact that *L. acidophilus*, the most widely consumed as well as studied due to its probiotic characteristics, forms the largest group within the LAB group, the majority of investigation in respect of probiotic species deal with this group. Notably, *Lactobacillus* goes to open the way for good flora dominance by inhibiting the growth of the pathogens. Such microbes are one of the most important probiotics, therefore generating lots of interest in the research on the human gastrointestinal microbiome, which is closely related to human health. *Lactobacillus* also functions to synthesize vitamins and amino acids that are essential yet, it facilitates the intake and absorption of minerals (Milani et al., 2017).

The word bifidobacterium is a translation of the genus of the bacteria which frequently possess the branching ends (the term " bifidobacterium " comes from the Greek word "bi" which means two and "defidia" which means splitting) (Henrick et al., 2018). It is the set of microorganisms that is essential physiological bacteria to the human health and are often found in large amounts in dietary supplements. For proper intestinal health, Bifidobacterium species can grow and metabolize in both the middle and end of the small and large intestine and adapt to being anaerobic, and also secrete bifidogenic substances specific to the type of probiotics (Bested et al., 2013). The diversity of the Bifidobacterium class, which currently consists of 32 species and nine subspecies, includes 14 species that were isolated by human feces (Klaassens et al., 2009).

Gram-positive parthenococci as well as *Enterococcus, Lactobacillus* and *Bifidobacterium* are extensively applied in food production. As a significant feature of *Enterococcus* strains that constitute a probiotic, they can concurrently coexist, compete, and adhere to cells in the digestive tract. Besides, *Enterococcus* has a great tolerance to a wide range of temperatures and pH values because of its ability to produce the bacteriocins, the natural antibacterial agent useful in the food sector (Hanchi et al., 2018).

As technology is advancing, *Saccharomyces cerevisiae* is used by the industries because of its historical safety record and the identification of favourable strains. For instance, *S. boulardii* are popularly used in the treatment of digestive disorders, among others, diarrhea symptoms. It has been thoroughly studied for its probiotic effect; it is beneficial when used with antibiotic therapy. Furthermore, it possesses immunomodulatory properties that help regulate immune pathways in the context of infectious or chronic conditions (Czerucka and Rampal, 2019). Other more widely available probiotic groups are S*treptococcus* species, *Bacillus* species, and *E. coli*, alongside the yeasts and *Enterococci* already discussed. The pictorial representation of probiotics diversity is shown in Fig. 1.

Prebiotics

According to previous investigations, prebiotics are oligosaccharide carbohydrates, primarily xylooligosaccharides (XOS), lactulose, galactooligosaccharides (GOS) inulin, and the fructose-oligosaccharides (FOS) (Yin et al., 2022). But recent investigation indicates that prebiotics aren't just carbs—they can also be other non-carbohydrate substances that comply with the prebiotic profile, like polyphenols that are extracted from fruits like blueberries 21 and black raspberries (Jiao et al., 2019). New prebiotic species are continually being generated due to ongoing optimization processes for prebiotic production; these mainly consist of polyphenols, polysaccharides, and polypeptide polymers, all of which have promising future directions for research. The pictorial representation of prebiotics diversity is shown in Fig. 2. The primary sources of emerging prebiotics are microorganisms from a variety of sources: fruit juices, waste products from fruits, algae, and herbal remedies (Rezende et al., 2021). Even while the understanding of these prebiotics is not as advanced as that of GOS and FOS, their potential warrants further investigation and appears to have an exciting future.

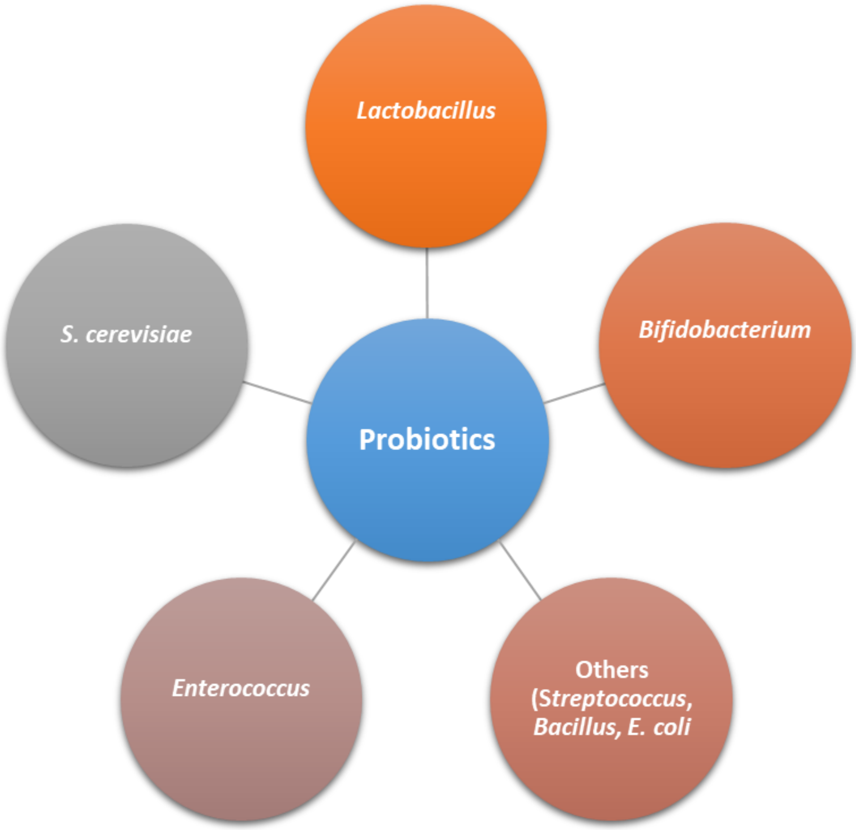

Fig. 1: A pictorial representation of probiotics diversity

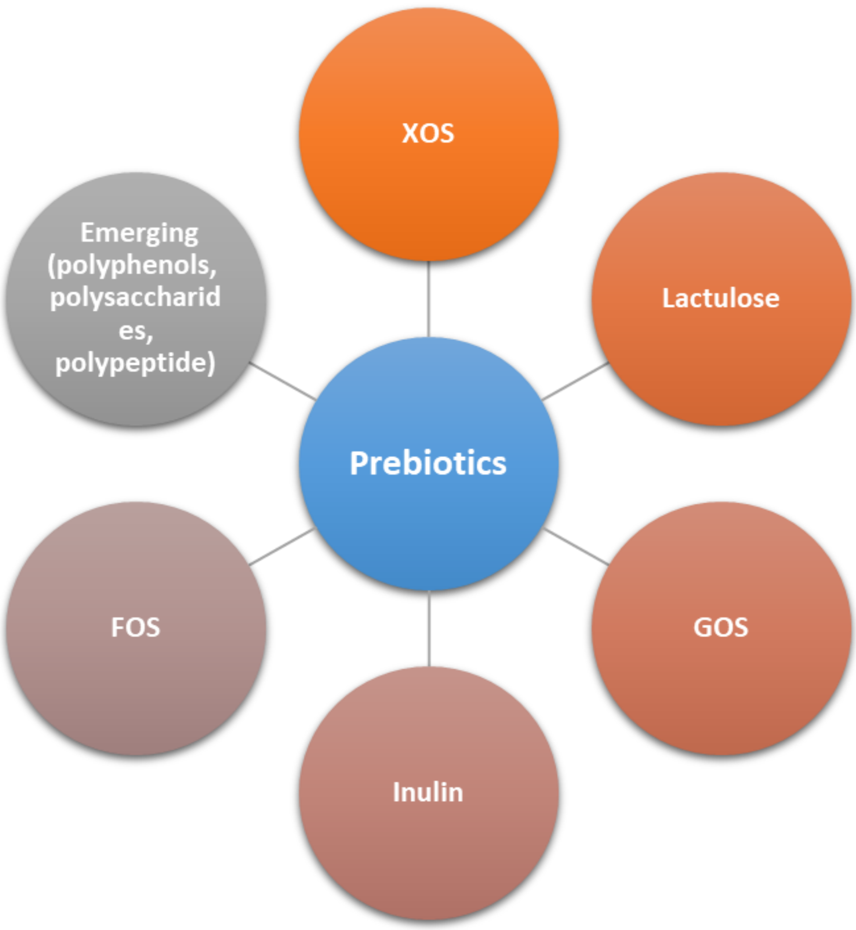

Fig. 2: A pictorial representation of prebiotics diversity

Harnessing the Potential of Probiotics

Probiotics, have recently been under focus for their benefits on the gut and now the researchers are looking into their effect on fertility. Recent findings propose that these beneficial microorganisms can help improve fertility and reproductive health in the male and female. Through enhancing hormonal balance and reproductive organs, probiotics could be a natural approach to treating several reproductive concerns.

Effect of Probiotics on Male Reproductive Health

Probiotics can definitely play a role in male reproductive health since they have a potential to enhance sperm quality and movement. They also aid in the regulation of the flora in the gastrointestinal tract with beneficial impact in relation to testosterone and reproductive system. Recent works have also indicated the benefits of using probiotics in reducing oxidative stress, inflammation and therefore male fertility.

Semen Quality and Spermatogenesis

Although, there is a lack of research on the effects of probiotics on male fertility. Probiotic strains, however, have been found to improve semen mobility and kinematic characteristics in vitro and in vivo, as well as in specific disease models. When *Lactobacillus rhamnosus* PB01 was added to diet-induced obese mice, the percentage of progressively motile sperm increased and there were beneficial implications for weight loss as well as reproductive hormones (Dardmeh et al., 2017). In asthenozoospermic males, on the other hand, *Lactobacillus* and *Bifidobacterium* improved sperm motility and decreased the percentage of DNA fragmentation in sperm. It was also discovered that mice fed alginate oligosaccharide, which promotes the growth of probiotic bacteria in the gut, had higher sperm quality and spermatogenesis after fecal microbiota transplantation (FMT) (Zhang et al., 2021).

Probiotic supplementation can improve spermatogenesis, testosterone levels, and seminiferous tubule cross-sectional profiles in aged mice, suggesting that probiotics may influence testicular function and therefore, semen quality (Poutahidis et al., 2014). Studies have suggested that the gut microbiota may be responsible for controlling the testicular function and also change the blood-testis barrier (BTB) permeability (Al-Asmakh et al., 2014). If the data above are proven to be so through further study, it might herald great advances in treating infertility. In this respect, various theories have emerged to explain better the role of probiotics in improving spermatozoa function. By conducting the in vitro experiment, Zhang et al. (2020) found out the inhibitory effect of the harmful species (*Pseudomonas aeruginosa*) and the helpful species (*Lactobacillus casei*) in the poultry serum. They found that, although *L. casei* treatment alone did not improve these parameters, it significantly lowered the decline in sperm motility and the impairment of mitochondrial activity caused by *P. aeruginosa*. This suggests that *Lactobacillus* may improve semen quality by resisting the detrimental effects of predominantly harmful bacteria on sperm.

More in vivo research has shown that probiotic administration may influence spermatogenesis and testicular function by altering the gut flora and serving as an antioxidant. Spearman's correlation analysis was used to examine the links between testicles and essential gut microbiota (Tian et al., 2019). According to studies, giving sperm *L. rhamnosus* CECT8361 and Bacteroidetes longum CECT7347 enhanced sperm motility, lowered sperm intracellular H2O2, and decreased DNA fragmentation. Therefore, by functioning as antioxidants, these probiotic strains may improve sperm quality (Valcarce et al., 2017).

Prostatic Health

The effects of probiotics on the prostate have been rarely examined, with only a few studies in recent years. Several in vitro experiments have shown that treatment of human prostate cancer cells with specific probiotic strains (*L. rhamnosus* GG, *L. acidophilus* La-05, *L. casei*-01, and Bifidobacterium animals Bb12) strongly induced apoptosis (Rosa et al., 2020), indicating the potential of probiotics to suppress prostate cancer. Furthermore, probiotics have been demonstrated to improve the prevention of episodes and alleviate symptoms in chronic bacterial prostatitis caused by *Enterobacteriaceae* (Chiancone et al., 2019). In addition, decreased bacterial load of *E. coli* and *Enterococcus faecalis* in urine cultures was observed after probiotic administration in prostatitis (Pacifici et al., 2021). However, no clear etiology exists for prostate disease; thus, the relationship between prostate microbiota, prostatitis, and prostate cancer, as well as the potential role of probiotics in alleviating them, is worth further investigation.

Effects of Probiotics on Female Reproductive Health

Follicular Dynamics

The impact of probiotics on follicular growth in women having healthy ovaries has not been extensively studied. In menopausal women, Probiotic supplements are believed to help prevent related symptoms, such as obesity and dyslipidemia, among others, by delaying the decline in estradiol production and ovarian activity. Probiotics derived from the feces of healthy women were given to ovariectomized menopausal rats and they settled in the gut, which changed some metabolites and increased estrogen circulation (Chen et al., 2021). Probiotics are found to profoundly impact the post-partum estrus in cows, particularly for the sows. The investigation revealed that sows with diverse parities (Hayakawa et al., 2016) would have shorter estrus intervals when using probiotics (single or in a cocktail). From these results, the probiotics could cause changes in weaning estrus periods through the regulation of hormone secretion or gut microbiota.

Placenta

During the fetus development, a transient tissue connected to the mother called placenta joins the fetus to the uterus. In order to support proper growth of the foetus, the placenta's function is to effectively transfer oxygen and nutrients from the mother to the foetus. Various published studies have shown that oral probiotics may play a role in the regulation of the placental function. Dietary intake of probiotics might result in altering the composition of the placental microbiota and thus have any impact on the placental function as the studies have revealed that probiotics are able to cross the placental barrier from the gut to amniotic fluid by genetically labeled *E. faecium* strain (Voreades et al., 2014). The in vitro studies proved that *L. rhamnosus* GR-1 decreased the secretion of TNF-α from human placental trophoblast cell following activation by lipopolysaccharide. Probiotics also play a special role in mitigating placental inflammatory responses, thereby minimizing the chances of developing severe preeclampsia (Brantsæter et al., 2011). Hence, the probiotics may influence the placental function by changing the microbiota profile, stimulating the immune system, and improving the placental metabolic regulation which might occur during pregnancy.

Pregnancy

Research has proven that expecting mothers, who take probiotic supplements, have improved metabolism and composition of gut microbiota that, in turn, have a direct impact on improved fetal development (Jarrett et al., 2019). The studies conducted on probiotics have evaluated a positive influence of the gut microbiota in the immune development of the fetus. Specific probiotics like *Bifidobacterium lactis*, *B. longum* and *L. rhamnosus* particularly, have been identified to show prominent changes in the expression of TLR-related genes in the fetal gut during the period of pregnancy (Rautava et al., 2012). Concerning the pigs after weaning, and neonatal piglet mortality rate, the maternal fetus growth during pregnancy defines also the birth weight (Rootwelt et al., 2012). Studies have demonstrated the probiotic treatment for pregnant sows during the last trimester of the pregnancy improves litter and the birth weight in sows of their early and a higher parity (Böhmer et al., 2006). Moreover, the concurrent use of Bacillus and prebiotics (isomaltooligosaccharide) has been reported in improving fetal growth, thereby enhancing serum levels of growth hormone (Gu et al., 2019) and the placental antioxidant capacity.

Reproductive Diseases

Probiotic consumption is recommended as a therapeutic strategy to modify the gut microbiota structure in the treatment of the PCOS (Shirvani-Rad et al., 2021). The results of a recent study show that the frequency of remission in PCOS can be reduced when FMT re-establishes eubiotics in the gut flora after dysbiosis (Corrie et al., 2021). This indicates the possibility of using beneficial probiotic bacteria in PCOS. Probiotics are believed to be one of the effective modalities of bacterial vaginosis (BV) treatment as they increase the rate of colonization of lactobacillus and help with the elimination of discomfort and the restoration of the vaginal flora. Oral administration of *L. crispatus* will contribute to the decrease of abundance in patients with BV after enteric probiotic administration (Rostok et al., 2019), and application of vaginal probiotic supplementation will help to colonization of *Lactobacilli* in BV patients, thus lowering vaginal pH and increasing the production of antimicrobial substances that both prevent probiotics have a long list of attributes as well on endometrium. A lab investigation demonstrated that endometrial epithelial cells wounded by HIV-1 could restore their barrier function when treated with probiotic *Lactobacilli* (Dizzell et al., 2019). Moreover, probiotics fortify the uterine barrier function and lower inflammation, which are key in preventing endometritis induced by *Staphylococcus aureus* (Hu et al., 2019). The functioning of *Lactobacillus* in managing the endometriosis-associated pain has been confirmed (Leonardi et al., 2020)). The research cited indicates that probiotic activate the epithelial integrity, restructure the endometrial biome and minimizes inflammation to cure endometritis and endometriosis, respectively.

Harnessing the Potential of Prebiotics

A healthy environment within the genital tract prevents infection and inflammation. It is currently understood that treating diseases and infections of the reproductive system requires restoring the balance of this intricate ecosystem. Employing probiotic bacteria, which promote the growth of advantageous microbes, can help accomplish this goal. Prebiotics that are intended to improve the state of resident microorganisms and used probiotics may also have an extra benefit. Table 4.1 summarizes the application of prebiotics to increase probiotic levels and eventually improve reproductive health.

Future Directions

In the field of reproduction, we are constantly amazed by the discoveries in prebiotics and probiotics that can benefit overall health. In the future, more attention should be paid to developing specialized interventions, tapping into the latest discoveries in microbiome science, and creating prebiotic and probiotic supplementations to suit individual microbiome composition. Besides that, more detailed clinical trials and studies would clarify the efficiency and safety of the treatments in different populations. The integration of microbiome engineering with precision synthetic biology and targeted therapy at the level of reproductive health challenges may be the future of reproductive health treatment, contributing to the development of therapeutics for reproductive diseases. In the end, the amusement of microbial matrimony, which deals with the combination of prebiotics and probiotics, depicts a new era in reproductive medicine. Exploiting the symbiosis among microbes and hosts which provides an all-round solution is a new method of optimizing reproductive health through genetic engineering. It is possible that the clinical practice will be transformed radically, thereby producing successful results for individuals globally.

Table 4.1: A Summary of Clinical Application of Prebiotics to Enhance Reproductive Health

Prebiotic Treatment	Specie	Clinical Effects	References
FOS+XOS	Pregnant women	Reduced oxidative stress, enhanced mitochondrial and cholinergic function in fetal and maternal brain	(Krishna et al., 2015)
XOS	Hy-Line brown laying hens	Increased ovarian weight and follicular size, increased level of reproductive hormones (LH, FSH, P4), improved lipid metabolism	(Wen et al., 2022)
Short chain GOS+ long chain FOS	Pregnant mice	Increased tolerogenic immune reaction, decreased Th-1 dependent delayed-type hypersensitivity response	(Van Vlies et al., 2012)
GOS	Pregnant women	Decreased level of LachnospiraceaeUCG_001 but increased level of Paraprevotella and Dorea. No significant effect on gestational week, birth weight, chest circumference, head circumference, and delivery mode	(Van Vlies et al., 2012)
Mannan-oligosaccharides (MOS)	Zebrafish	Increased sperm production, no significant effect on oocyte maturation and levels of 17b-estradiol and testosterone.	(Forsatkar et al., 2018)
MOS	Male Rats	Decreased level of corticosterone, increased level of testosterone, increased seminiferous tubules' radii and sperm production	(Rodrigues et al., 2021)
Bovine lactoferrin+*L. acidophilus* La-14+*L. rhamnosus* HN001	Women	Increased levels of vaginal *L. acidophilus* and *L. rhamnosus* on days 14 and 21	(De Alberti et al., 2015)
Bovine lactoderrin+*L. acidophilus* GLA-14+ *L. rhamnosus* HN001	Women	Decreased vaginal pH, decreased vaginal discharge, itching and fishy odor, increased vaginal colonization of these two probiotics	(Russo et al., 2018)
Lactoferrin	Women	Optimization of vaginal flora (significantly increased level of *Lactobacillus*)	(Otsuki and Imai, 2017)
Lactoferrin	Women	Increased level of vaginal *Lactobacillus helveticus,* decrease in the levels of bacterial species causing BV, decreased vaginal pH	(Pino et al., 2017)
Lactoferrin	Women	Increased level of vaginal *Lactobacillus*	(Otsuki et al., 2014)

Conclusion

There has been growing interest in the link between the microbiome and reproductive health, and probiotics as therapeutic candidates. There are different microbes in female and male reproductive systems, which proves that the gut microbiome affects reproductive health. Probiotics offer potential for promoting health and reducing disorders, as dysbiosis correlates with adverse pregnancy outcomes. They modulate bacterial concentrations, control the metabolic rate and are involved in immune defence mechanisms. Prebiotics work hand in hand with probiotics in that they support growth of desirable bacteria. In males, probiotics positively affect sperm characteristics such as quality, motility and testicular functionality, while in females, they help maintain estradiol levels and promote normal growth of the follicles in addition to enhancing the functionality of the placenta. Specifically, prebiotics such as oligosaccharides promote probiotic activity, anti-oxidant protection, and hormonal balance. Subsequent studies should concentrate on specific therapy for the specific microbial composition, advancing microbiota modulation to precision medicine, and performing clinical trials on safety and efficiency in relation to infertility, which can expand the opportunities for solving reproductive issues.

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