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New insight about the role of microbiome and probiotics in female reproduction: A review 6

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Abstract
Background: The study of the microbiome in regard to human health and disease, particularly in reproductive health, is still a very nascent field of research. This article proposes to enhance understanding of the microbiome of the reproductive tract, that can help improve the handling of reproductive dysfunctions caused by dysbiosis.
The disturbance of the microbiota in the uterus and cervico-vaginal area of women has been linked to various gynecological conditions, including polycystic ovary syndrome, endometriosis, non-cyclic pelvic discomfort, and infertility. Global prevalence of female infertility is 12.5%.
A novel point of view is arising on the significance of microbiomes of the uterus and vagina especially the context of reproductive health. Recent studies have demonstrated that the targeted use of specific probiotics, often in conjunction with prior antibiotic therapy, can help restore a healthy balance of beneficial microorganisms in the body. This restoration of symbiotic microbiota has been found to enhance the chances of successful conception and improve outcomes in assisted reproductive technology.

Keywords: Female reproductive health, microbiota, microbiome, probiotic, infertility

Introduction

Approximately 80% of women of reproductive age harbor a vaginal microbiota community that is primarily made up of Lactobacillus species. This composition serves as a dependable indicator of a healthy and balanced vaginal ecology (Pendharkar *et al*., 2023) [29].
Specifically, the study by (Ravel *et al*., 2011) [25], identified four predominant species, namely *L. crispatus*, *L. iners*, *L. gasseri*, and *L. jensenii*, in asymptomatic women of reproductive age.
The colonization of the reproductive system by Lactobacillus starts during puberty when there is exposure to estrogen. This colonization subsequently goes through significant changes until menopause.
Hong and colleagues performed an extensive examination of the vaginal microbiome, encompassing 3277 women who were experiencing primary and/or tubal infertility. (Hong *et al*., 2020) [30] Their analysis was based on classifying the samples of the vagina's microbiota into two categories: high-Lactobacillus and low-Lactobacillus vaginal microbiota. Women were categorized as being in the high-Lactobacillus group if they exhibited a Nugent score between 0 and 3, a negative Amsel/Spiegel's test, or if the dominant bacterial species in their vaginal population was *Lactobacillus* spp. as determined by a 16S rRNA gene sequencing approach. Otherwise, they were categorized as part of the low-Lactobacillus group. The utilization of a consistent model for estimating the general relationship revealed a noteworthy adverse correlation between an increased number of Lactobacillus species and infertility (odds ratio 0.83). This suggests that a healthy vaginal microbiota is linked to a decreased likelihood of experiencing infertility (Hong *et al*., 2020) [30].
In a healthy female, the usual composition of bacteria in the vagina is primarily made up of *Lactobacillus* spp. (Ravel *et al*., 2011) [25], Nevertheless, the microbiome environment can be influenced by factors including age and hormonal alterations (Gajer *et al*., 2012) [10]. In infants, the vaginal flora consists of a mixture of aerobic and anaerobic microorganisms, including Enterobacteria, Prevotella, Staphylococcus, and Streptococcus strains (Huang *et al*., 2014) [14]
Subsequent changes during puberty cause the vaginal environment to change into estrogenic, resulting in an increase in glycogen levels and a decrease in pH levels. The primary bacteria responsible for this is Lactobacilli.

Microbiome alterations in physiological and pathological conditions

The latest study by (Schoenmakers *et al*., 2019) [26] has found a correlation between the microbiota and the outcome of fertilization and the ongoing development of early pregnancy. An in-depth comprehension of the fluctuations in the microbiome associated with reproductive problems can provide valuable insights for developing advanced therapeutic approaches that could potentially improve the outcomes of earlier untreatable medical disorders.

It is crucial to acknowledge that the association between the microbiome and the müllerian system is likely more intricate than just the existence or lack of particular microbes, or even their amount in the tissues (Franasiak and Scott, 2015b) [9]. Future studies should investigate the microbial interactions responsible for the formation of various biofilms and their subsequent effects on physiology of the reproduction. The microbiome within the Paramesonephric ducts has the capacity to impact the reproduction process and may modify gametogenesis (Habiba *et al*., 2021) [13]. Indeed, ovarian follicles have been found to have active microbiomes (Franasiak and Scott, 2015b) [9]. The microbiome not only affects the müllerian system, but it also influences the reproductive axis and perhaps impacts gamete production (Franasiak and Scott, 2015a) [8]. It might be probable that ovarian follicles harbor a functional microbiome. Studies have demonstrated that certain bacteria can exert detrimental effects on the formation of follicles and may even restrict the response of gonadotropins in certain women (Dutta *et al*., 2019) [6].

The majority of research investigating the impact of the microbiome on ART and clinical outcomes consists of association studies (Franasiak and Scott, 2015b) [8] (Diaz-Martínez *et al*., 2021) [5] (Bernabeu *et al*., 2019) [2]. Thorough analysis of the mechanisms involved is necessary in order to discover new approaches for therapy.

The researchers proposed that the vaginal microbiota, which changes over the menstrual cycle due to varying estrogen levels, would also be affected by the controlled ovarian hyperstimulation required for successful IVF (Nunn and Forney, 2016, Hyman *et al*., 2005) [22, 15].

Multiple research investigations have demonstrated a correlation between infertility in women and an increased likelihood of experiencing BV, a condition associated with late fetal mortality and pre-eclampsia. However, there is no scientific evidence to support the claim that BV has a negative impact on the outcome of pregnancy, as indicated by studies conducted by (Ralph *et al*., 1999, Gaudoin *et al*., 1999) [24, 11]. Previous research has revealed that approximately 40% of women undergoing IVF therapy exhibit aberrant microorganisms in their vaginal system (Leitich and Kiss, 2007, Leitich *et al*., 2003) [21, 20].

Chronic endometritis

Chronic endometritis (CE) is the most common pathogenic event related to endometrial bacteria. Endometrial inflammation can be triggered by various bacteria such as Enterococcus faecalis, Gardnerella vaginalis, *E. coli*, *Klebsiella pneumonia*, *Pseudomonas* spp., *Proteus* spp., *Staphylococcus* spp., *Streptococcus* spp., in addition to reproductive tract infectious agents such as Mycoplasma and *Ureaplasma* spp., and yeasts such as *Candida* spp and *Saccharomyces cerevisiae*. These microorganisms are the distinguishing factors in endometrial inflammatory processes (Greenwood and Moran, 1981, Cicinelli *et al*., 2009) [12, 3]. The prevalence of CE in the general population is approximately 19% (Yoshii *et al*., 2013) [28], however in the infertile population, it is more than forty-five percent (Kushnir *et al*., 2016) [19]. Despite the higher frequency, it is believed that RIF and RPL are more strongly associated with infertility compared to other reasons for infertility (Johnston-MacAnanny *et al*., 2010, Cicinelli *et al*., 2015) [16, 4].

The exact cause of endometriosis remains unknown, even after conducting basic investigations. Multiple investigations indicate that uterine bacterial infections can cause endometriosis. A study conducted by (Alahmar *et al*., 2019) [1]. Discovered elevated levels of *E. coli* bacteria in the menstrual blood of women with endometriosis. The researchers also identified Gardnerella, Streptococcus, Enterococcus, and Staphylococcus as the most commonly identified pathogenic genera in endometrial specimens from women with endometriosis. Conversely, a different group of microbiotas including Actinomyces, Corynebacterium, Prevotella, Fusobacterium, and Propionibacterium were primarily found in the control subjects, while *Lactobacillus* spp. was predominantly observed (Khan *et al*., 2014) [17]. Consistently, microorganisms belonging to the Staphylococcaceae and Streptococcaceae families were shown to be significantly more prevalent in the cyst fluid of women with ovarian endometriosis compared to the control group (Khan *et al*., 2016) [18]. The results indicate a strong association between CE and endometriosis, as demonstrated by (Khan *et al*., 2016, Takebayashi *et al*., 2014) [18, 27]. It is possible that the introduction of endometrial cells into the abnormal endometrium may have caused dysperistalsis and a decrease in contractions in the uterus in women with CE, as suggested by (Pinto *et al*., 2015) [23].

Utilizing microbiota to enhance outcomes for reproduction

The human microbiota refers to the assemblage of microorganisms, such as bacteria, viruses, and fungi, that inhabit and reside inside the human body. These microbes play vital functions in preserving health, and disruptions in the microbiota may be linked to several disorders. There has been an increasing focus on studying the influence of bacteria on reproductive health and enhancing outcomes of reproduction in recent decades.

In the late twentieth century, Egbase *et al*. presented a compelling argument for the significance of the reproductive tract's microbiota in achieving successful reproduction. Following the retrieval of oocytes and 48 hours following the transfer of embryos, the researchers examined the bacteria present at the tip of the transfer catheter. They contrasted the findings of a simulated transfer performed with preventive antibiotics to the outcomes of pregnancy (Egbase *et al*., 1999) [7].

Purpose

- We've summarised the latest information regarding how the vaginal microbiota is affected by the menstrual cycle and sexual hormones, based on previous knowledge hormones,
- Reproductive microbiome has the potential to impact the likelihood of infections and diseases, negative consequences during pregnancy, and the efficacy of fertility therapies.
- Role of probiotics in enhancing reproductive outcomes

Conclusion and future perspectives

The existence of particular microbiota in the reproductive tract, without regard to their ability to cause disease, or the modification of the microbiota that naturally reside in the reproductive tract, might cause problems with fertilization, implantation, pregnancy, and embryo development. This might lead to a decline in the number of live births and the unsuccessful outcome of fertility therapies.

Conflict of Interest
Not available

Financial Support
Not available

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