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Review Article

Endometrial Microbiomes and Gynecological Diseases; Between Knowledge and Practice. Opinion Article

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Abstract

The application of next-generation sequencing (NGS) methods in studying microbial RNA transcripts provides more understanding about healthy endometrium and uterine dysbiosis related to many gynecological problems. The aim of this opinion article is to assess the benefits and limitations of applying this new knowledge and the future areas for researches. A search of the academic literatures was conducted in various databases and studies published in the last 10 years related to our objectives were included. In conclusion, due to the low- biomass microbial site of the uterus, more studies are essential after establishing standardized methods for analysing these microbial taxa in order to avoid the risk of contaminations. Many studies recommend the use of antibiotics, probiotics or prebiotics as a treatment, yet; there is no evidence based pathway for managing cases with proven uterine dysbiosis.

Keywords: *Uterine Microbiomes; Homeostasis; Dysbiosis; Probiotics; Microbial Transplants*

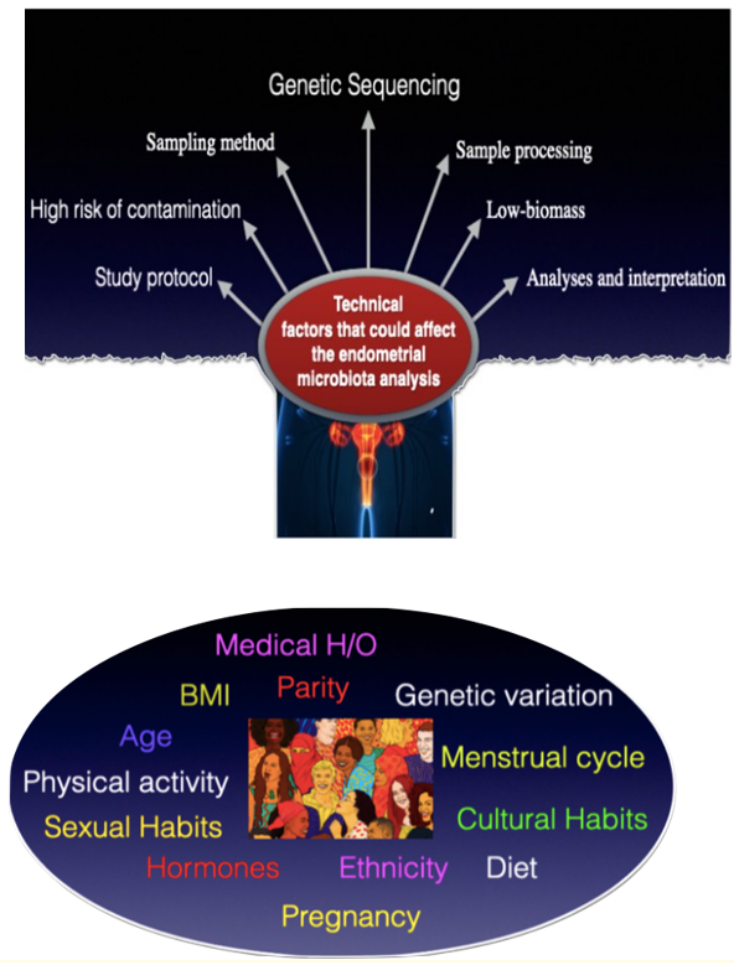
Introduction

Over the last decade, uterine microbiota has become an area of massive studies due to it is significant role in endometrial homeostasis, by production of bioactive molecules regulate the metabolism, physiology and immune functions. The application of next- generation sequencing (NGS) methods, such as metatranscriptomics which analyses microbial RNA transcripts, reveals more knowledge of possible functionally active microbiomes associated with healthy endometrium and uterine dysbiosis in many gynecological problems; infertility, chronic endometritis, endometrioses, adenomyosis, endometrial hyperplasia and endometrial cancer.

Uterus homeostasis and function of uterine microbiomes

Microbiome is a group of microorganisms that inhabit a particular organ in our body, such as; uterus, vagina, intestine, or skin. It is essential for developing the human health and immunity against disease, as it can secrete bioactive molecules regulate the body metabolism and physiology. They are not invaders but beneficial colonizers, which could harm if any alteration of its function happened (dysbiosis). Many researches suggest that vaginal microbiome affecting the uterine microbiome, considering that *Lactobacillus* species is the dominant bacteria inside the endometrium as well as the vagina.

Technical and individual factors that could affect the endometrial microbiota analysis



Objectives of the Study

1. Identify the healthy uterine homeostasis and how it could be altered.
2. Check the correlation between different types of microbiomes and gynecological conditions.
3. Assess the recent approaches for treating uterine dysbiosis.
4. Assess the benefits and limitations of applying this new knowledge and the future areas for researches.

Methods

A search of the academic literatures was conducted in various databases including Cochrane Library, Pubmed, Web of Science, Trip database and Clinical key web sites. Studies published in the last 10 years related to our objectives were included.

The initial search found 341 articles, of which 237 full manuscripts were reviewed after removal of duplicates, 28 articles were eligible for inclusion. Data related to the uterine microbiota, reproductive outcome and endometrial pathologies were analyzed and summarized.

Healthy endometrium predominant taxa

Lactobacillus, Bifidobacterium, Blautia, Corynebacterium, Propionibacterium, Acinetobacter, Bacillus, Barnesiella, Pseudomonas, Ralstonia, Shigella, Staphylococcus, Desulfosporosinus, Enterobacter, Escherichia, Fusobacterium, Gardnerella, Jonquetella, Parabacteroides, Prevotella, Streptococcus.

Uterine dysbiosis and unhealthy microbiomes in the uterus: Infertility predominant taxa

Atopobium, Bacteroides, Betaproteobacteria, Bifidobacterium Burkholderia, Chitinophagaceae, Corynebacterium, Escherichia/ Shigella, Flavobacterium, Gardnerella, Lactobacillus, Megasphaera, Pelomonas, Prevotella, Pseudoalteromonas, Rhodanobacter, Sneathia, Staphylococcus, Streptococcus.

Lactobacillus dominance, more than 90%, associated with better outcome of clinical pregnancy and live birth rates in the infertility population undergoing IVF.

Endometrioses predominant taxa

Acinetobacter, Barnesiella, Comamonadaceae, Enterobacteriaceae, Flavobacterium, Gardnerella, Lactobacillus, Moraxellaceae, Prevotella, Pseudomonas, Sphingobium, Staphylococcaceae, Streptococcaceae, Vagococcus.

There are two main roles of the microbiome in the endometriosis: estrogen detoxification and immune regulation. Other hypothesis is that uterine dysbiosis can trigger the inflammatory cascade that can lead to progress of endometriosis. It is well established that endometriosis closely related to the chronic inflammatory state.

Chronic endometritis taxa

Alteromonas Anaerococcus, Atopobium, Bifidobacterium, Dialister, Gardnerella, Lactobacillus, Megasphaera Parvimonas, Prevotella, Propionibacterium Streptococcus, Veillonella.

Chronic inflammation of the endometrium (CE) is caused by the presence of bacterial pathogens in the uterine cavity and is related to repeated implantation failure and repeated miscarriage.

Endometrial cancer taxa

Acinetobacter, Anaerostipes, Anaerotruncus, Arthrospira, Atopobium, Bacteroides, Cloacibacterium, Comamonadaceae, Dialister, Escherichia, Peptoniphilus, Porphyromonas,Pseudomona, Ruminococcus, Treponema.

In endometrial cancer there is a different microbial taxa distinguishable from the benign cases.

Endometrial polyps taxa

Alteromonas, Bifidobacterium, Euryarchaeota (*Archaea*) *Gardnerella, Lactobacillus, Streptococcus*.

Dysfunctional menstrual bleeding

Gardnerella, Lactobacillus, Prevotella, Sneathia, Veillonella.

Chronic stimulation inflammatory reaction in the endometrium could result in developing endometrial polyps and abnormal uterine bleeding.

Current treatment

There is no clear guidelines for evaluating the endometrial microbiota, and for treating the uterine dysbiosis.

Probiotics

Probiotics role in modifying uterine homeostasis is one of the new frontier in women health, yet, we need to consider that probiotics are not medical drugs and only few studies were done to investigate it is efficacy [1]. Modification of female reproductive tract microbiome play a significant role in maintaining the immune profile, which could be used to protect against different infections. Recently, studies showed that probiotic including lactobacilli (RC-14 and GR-1) can enhance endometrium barrier function and protect from human immunodeficiency virus-1 (HIV-1) [2].

Prebiotics

Prebiotics are source of nutrients for the host beneficial microbiome, as the body cannot digest them, they can reach to the lower digestive and genital tract. Lactoferrin is one of common prebiotic agents, was administered to patient with chronic bacterial vaginosis, leading to improving pregnancy and live birth rate, in those with history of preterm birth [3].

Microbial transplants

Faecal microbiota transfer (FMT) has been used for treating different conditions, with solid evidence only for efficacy in treating recurrent *Clostridioides difficile* infection. There are many ongoing studies searching the usage FMT for various indications.

Vaginal microbiota transplants (VMT) is one of the new frontiers in microbial transplants and reproductive health. By transferring healthy donor cervico-vaginal fluid to diseased women, with aim to restore the proper vaginal homeostasis. Lev-Saige., *et al*. reported positive outcome when the tested using VMT from healthy donors to treat women with symptomatic and recurrent bacterial vaginosis [4]. VMT seems to be a promising area for more randomized controlled trials to test it is effectiveness in managing uterine dysbiosis, as it is well established now that uterus colonized by microbiome ascending from the vagina and the cervix. Other area to be studied, which could open a gate for infertility treatment is uterine microbiota transfer.

Dysbiosis and infertility

What we all know is that antibiotics can alter the microbiota composition in the reproductive system. Kokyono., *et al*. used broad spectrum antibiotic, levofloxacin and amoxicillin, to alter the endometrial microbiota from the non-dominant into dominant *Lactobacillus*, followed be adding probiotics, in 53% of the patients who reached to *Lactobacillus* dominant state in the uterus, they showed higher

non statistical significant pregnancy rate when compared to the non-*lactobacillus* dominant group. In another trial to modify uterine dysbiosis among women undergoing infertility treatment, by using oral lactoferrin, a prebiotic agent, for three months after treatment with antibiotics, the results showed that 67% (6/9) of the patients reached to *Lactobacillus* dominance state [6].

In endometriosis, prophylactic administration of antibiotics before egg retrieval in cases with severe endometriosis and endometrioma is a common practice today, to decrease the risk of infection. The significant of that started to encourage many to study about the effectiveness of antibiotic, pro-biotic and prebiotic as a possible treatment for the endometriosis. For instance, an experiment on mice showed decrease of endometriosis size in mice after receiving metronidazole antibiotic. Another recent study on human suggested decrease of endometriosis pain when giving oral probiotic containing *Lactobacillus* [7]. Currently, we are certain about the correlation between microbiomes and endometriosis flare but we do not know until now, what is the specific kind of treatment, antibiotic or probiotic to resume the balanced microbiome environment. It is the new frontier for treating and preventing endometriosis as well as many chronic women health.

Conclusion

There is lack of evidence about the endometrial dysbiosis; is it the cause or the results of the diseases. Many studies recommend the use of antibiotics, probiotics or prebiotics as a treatment, yet; there is no evidence based pathway for managing cases with proven uterine dysbiosis. Due to the low- biomass microbial site of the uterus, well-controlled studies should be conducted after establishing standardized methods for analysing these microbial taxa in order to avoid the risk of contaminations.

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