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Review article

Female reproductive tract microbiome in gynecological health and problems

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ABSTRACT

Microbes are intimately associated with human existence and health. Gut, oral cavity, skin, respiratory and urinogenical tracts are the major body sites inhabited by large consortia of microorganisms; each with specific composition. Application of high throughput genomic technologies has paved ways to gain an improved knowledge about the composition of the resident microbes and the ecosystem homeostasis and underscores the concept that dysbiosis of the flora may lead to predisposition to infection and diseases. Successful human reproduction owes an immense debt to this microbial community. Microbial communities exist throughout the entire length of the female reproductive tract at variable composition and density and play a role in gametogenesis, reproductive cyclicity, pregnancy and successful delivery of newborns. This review focuses on the recent studies from all over the globe on the composition of microflora in the female reproductive tract, their spatio-temporal diversity across the age of women and how the host–microbe collaboration is pursued to maintain reproductive efficiency. A special emphasis has been placed on the disruption of the stable flora and its association with the microbial imbalance and infections in bacterial vaginosis, endometriosis and pre-term birth. Finally, this article highlights that the restoration of normal microbial flora might provide a long-term therapeutic measure for the reproductive failures and endow with solutions to the global problem of reproductive failure, preterm birth and neonatal deaths.

1. Introduction

The extra-ordinary power of genomic technologies has convincingly demonstrated that under natural conditions, microbes do occur in a "consortium" where the interactions among different members cumulatively result in a system-level community behavior which is more than a mere addition of their activities together.[1] Presence of an incompatible member or intrusion by a pathogen can disturb the compactness of the organization and bring about a loss of homeostasis. Microbe–microbe interaction includes physical contact, chemical and metabolic exchanges.[2] Division of labor among the microbes is another attribute of the consortia which maintains the well coordinated functioning of the system. The consortium has an advantage over a single species in regard to executing a complex function and achieving endurance against the consistently shifting milieu.[3] Studies have also shown that in comparison to mono-cultures, a community is better suited to resist invasion by other organisms and combat different kinds of stresses.[4] A vast spectrum of research is thus ongoing to uncover the constitution and basis of microbial ecosystem in a wide variety of environmental and biological systems.

The human body is a home to an extraordinarily diverse population of microbes. As unearthed by Human microbiome projects, there exists intriguing patterns of microbial coexistence, breaching of which leads to diseases in many cases. As early as in 17th century, Antonie van Leeuwenhoek first described that the human body harbored bacteria.[5] Today we know that the microbial genes in the human gut alone (3.3 million) outnumber the protein-coding genes (20,000–50,000) of the human genome.[6,7] Humans have co-evolved with trillions of microorganisms that inhabit the body in a complex habitat-specific manner and are attuned to factors related to host physiology, age, diet, environmental conditions and the history of exposure to microbes.[8–10] Due to

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its immense impact on host metabolism and immune system, human metagenome is often regarded as the "second genome".[11–13] Microbial populations differ markedly between different anatomical sites such as skin, oral cavity, gastrointestinal (GI), respiratory and urogenital tracts and within the various microniche of a given site. Besides, they regularly show a large degree of interpersonal variation even in the absence of any diseases.[14] It is thus difficult to define a "healthy core human microbiome".[15] Despite this ambiguity, an overall alteration in the microbial profile of an individual has been well linked with a number of pathogenic states including cardiovascular diseases, type 2 diabetes, obesity and metabolic disorders and infertility.[11,16–21] The association of microbes with various reproductive complications has been suspected even before the first success of in vitro fertilization. However, due to paucity of data, this hypothesis remained unexplained till the characterization of microbiome from the reproductive tract.

Almost all facets of human reproduction from gametogenesis, to fertilization and embryo migration, to implantation with implications in early pregnancy failure or loss, and poor obstetric outcomes during gestation and parturition in terms of intrauterine infection and preterm birth are affected by the resident microbiota.[11] Researches focusing on microbial communities that inhabit along the male and female reproductive tracts and exhibit symbiotic, mutualistic and pathogenic relations with the host have been intensified.[22,23] We present herein a synthesis of research findings deposited over the last one decade on female reproductive tract microbiota, native and dysbiotic, to help the readers ask questions that are worthy of exploration in order to solve various complications related to female reproductive health.

2. Indigenous microbiota in female reproductive system

Urogenital tract microbiome makes up 9% of the total human microbiome.[23] Colonization of microbes in the human body commences after the delivery when new born comes in contact with the maternal womb, vaginal, fecal and skin microbes.[24,25] The main force that triggers the postnatal immunity is derived from this colonization.[26] Certain microbial species (*Escherichia coli*, *Escherichia fecalis* and *Staphylococcus epidermidis*) have been isolated from the meconium of healthy neonates born to healthy mothers within two hours of delivery indicating that the transfer of bacteria from the maternal body initiates through the amniotic fluid to the fetal circulation during gestation.[27] With the advent of genomic technologies, myriad of non-*Lactobacillus* sp. have been identified with definitive roles in maintaining reproductive fitness, in addition to *Lactobacillus* sp. which is historically regarded as the species of dominance in female urinogenital tract.[28]

2.1. Microflora of vagina

Vaginal microenvironment is a dynamic ecosystem with major capability of maintaining a healthy reproductive environment.[29] It is affected by a number of endogenous (e.g. age, physiology, body size) and exogenous (e.g. mating behavior, substrate use and routine-association with microbes) factors. About 250 bacterial taxonomic units have been identified from the vagina of women of various ages, health status and countries of origin.[30] Microbes mainly reside in the vaginal stratum corneum, the cornified epithelium that forms loose glycogen-filled cells without nuclei and thereby fail to recognize the foreign pathogens.[31]

Recent next-generation sequencing and metagenomic analyses have revealed that the vaginal microbiome harbors a high proportion of *Firmicutes* and a low percentage of *Proteobacteria*, *Bacteroidetes*, *Fusobacteria* and *Actinobacteria*. Vaginal microbiota belong to seven community types (I–VII) of which majority (types I, II, III and V) predominated by one or more species of *Lactobacillus*. Frequently detected members include *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus iners* and *Lactobacillus jensenii*. A prevalence of *Lactobacilli* was identified in a cohort of asymptotic North American women from Asian, African, Hispanic and Caucasian ancestries. Four of five clusters of microbiota observed in this study were dominated by *Lactobacillus* sp. whereas the fifth group comprised a higher proportion of obligate anaerobes.[32] A study from Indianapolis, USA, reported that *Lactobacillus* sp. formed a major phylotype in the vagina of 70% of the adolescent girls even before the onset of menarche.[33] A predominance of lactic acid producing bacteria such as *Lactobacillus*, *Streptococcus*, *Aerococcus* and *Facklamia* was also detected in the girls of age 13–18 from Uganda.[34] According to another study, women of European ancestry harbored a *Lactobacillus*-dominated microbiome while African-American women exhibited a diverse microbial profile.[35] Several studies from India and China demonstrated different strains of *Lactobacillus* sp. cohabit the vagina of the adult women of reproductive age while post-menopausal women formed a consortium composed mainly of *E. coli*, *Streptococcus* sp., *Prevotella* sp., *Bacteroides fragilis* and lactic acid producing *Veillonella* sp. and *Anaerococcus lactolyticus* in addition to *Lactobacilli*.[36–38] In 20–40% of the women who lacked vaginal *Lactobacillus*, variable proportions of *Acinetobacter*, *Acidovorax*, *Anaerococcus*, *Atopobium*, *Anaerococcus*, *Cloacibacterium*, *Coriobacter*, *Corynebacterium*, *Diaphorobacter*, *Eggerthella*, *Finegoldia*, *Gardnerella*, *Megasphaera*, *Mobiluncus*, *Peptoniphilus*, *Peptostreptococcus*, *Prevotella*, *Sneathia*, *Staphylococcus*, *Streptococcus*, *Ureaplasma*, *Veillonella* were detected.[39] This group of non-*Lactobacillus* sp. influences the vaginal health through the production of short-chain fatty acids (SCFA) and other low molecular weight compounds.[29] Interestingly, there is a remarkable difference in the genetic and metabolic potentials of the vaginal and non-vaginal *Lactobacilli* in humans.[30] Vaginal species have small genomes, high GC content and produce many differentially induced proteins in comparison to their non-vaginal counterparts.[40]

Among the vaginal *Lactobacilli*, *Lactobacillus crispatus* and *Lactobacillus iners* are the main producers of D-lactic acid and responsible for maintaining an acidic environment (pH 4.5–5.0).[30,32] Estrogen has a role in *Lactobacillus* dominance. It converts columnar epithelium into a thick layer of squamous stratified epithelium and increases the glycogen content for the growth of *Lactobacilli*. Maternal estrogen transferred to newborn increases the availability of glycogen in the vagina of an infant which is metabolized to lactic acid by *Lactobacillus* sp., within one day of birth. In addition to *Lactobacilli*, *Corynebacteria*, *Staphylococci*, *Streptococci* and *E. coli* are capable of degrading glycogen to lactic acid in the newborn within two hours of delivery.[41] A sharp contrast in the vaginal flora is noted between babies delivered through vagina, who inherit microbes from maternal vagina, and the cesarean baby whose microbial composition resembles that observed in the adult skin. Although the initial colonization by microbes in the vagina of an individual depends on the mode of her birth, microbial composition is eventually regulated by the level of estrogen which varies as a function of her age. Vaginal pH gradually decreases as the level of estrogen rises from puberty and this low pH is maintained throughout the reproductive age along with abundance of *Lactobacillus* sp. This correlation was reflected even in small time scale of menstrual cycles when the population too undergoes a temporal variation.[42] Due to lower dominance of *Lactobacillus* sp., juvenile and the pre-menarchal vagina are, in general, neutral or alkaline. Acidic pH prevents the growth of various pathogens including human immunodeficiency virus, yeast, *Neisseria gonorrhoeae*, *Atopobium*, *Megasphaera*, *Mobiluncus*, *Prevotella*, *Sneathia* and *Gardnerella vaginalis* (*G. vaginalis*), the