

Review

What fertility specialists should know about the vaginal microbiome: a review

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KEY MESSAGE

The vaginal microbiome composition varies between women, and has the capacity to fluctuate throughout a woman's life. The abundance of various bacterial species in the vagina greatly impacts a woman's reproductive health and pregnancy outcomes. The vaginal microbiome may be altered by exogenous factors that may impact reproductive health outcomes.

ABSTRACT

Our understanding of the composition of the microbial communities that inhabit the human body, known as the 'microbiome', is aided by the development of non-culture-dependent DNA sequencing. It is increasingly apparent that the balance of microbial species greatly affects the health of the host. Disturbances in the composition of bacterial communities have been shown to contribute to various disease states, and there is a growing body of evidence that the vaginal microbiota, which is unique to each woman, plays an important role in determining many facets of reproductive health. The purpose of this review is to investigate what is currently known about the composition of the vaginal microbiome, including what is considered 'normal' in terms of bacterial species and abundance. We will investigate the impact of vaginal microbiome composition on reproductive outcomes within the context of infertility treatments, and the implications this has been shown to have on assisted reproductive technology procedures.

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Introduction

The sequencing of the human genome in 2001 (Venter et al., 2001), while a notable achievement in the biological and physiological worlds,

is considered by some to be only a partial physiological blueprint for humans. The human microbiota, i.e. the community of microorganisms that populate us, both inside and out, is understood to contribute to this blueprint, and plays a significant role in determining the health status of the individual. Until recently, the primary focus

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Table 1 – Definitions.

Term	Definition
Microbiota	The microbial taxa that are associated with an environment and are revealed using molecular techniques such as 16S rRNA sequencing [Cho and Blaser, 2012; Ursell et al., 2012].
Microbiome	Refers to the habitat as a whole, thus incorporating the biotic and abiotic factors, encompassing host and microorganism genomes and environmental conditions [Cho and Blaser, 2012].
Metagenome	The collection of genomes and genes from the inhabitants of a microbiome [Marchesi and Ravel, 2015].
Metatranscriptome	The total content of gene transcripts in a community at a specific sampling time [Parro and Paz, 2015].
Metaproteomics	Interrogation of the entire protein complement of a community at a given time point [Wilmes and Bond, 2004].
Culturomics	Method allowing the determination of microbial community composition by high-throughput culture [Greub, 2012].
Biofilm	A structured consortium attached to a living or inert surface formed by microbial cells adherent to each other and surrounded by the self-produced extracellular polymeric matrix [de la Fuente-Nunez et al., 2013; Hall-Stoodley et al., 2004].
Dysbiosis	Qualitative and quantitative changes, their metabolic activity and their local distribution [Holzapfel et al., 1998].
Probiotic	Live microorganisms which when administered in adequate amounts confer a health benefit on the host [Sanders, 2008].
Prebiotic	A non-digestible food ingredient that benefits the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health [Gibson and Roberfroid, 1995].

rRNA = ribosomal RNA.

of human microbial characterizations has been within the context of a disease state; however, it is now recognized that the indigenous microbiota also serve to maintain human health [Zhou et al., 2010].

Prior to the advent of high-throughput DNA sequencing, culture-based methods were employed to identify bacterial species found in the body. However, comprehensive large-scale microbiome sequencing has been facilitated by advances in gene sequencing in the past two decades [Gonzalez et al., 2011; Peterson et al., 2009]. Thus, culture-based data, while still informative, must be interpreted within the limits imposed by those paradigms. They detect only a small proportion of (mostly aerobic) organisms, and are not truly representative of the clinically relevant spectrum.

Most bacterial communities coexist in mutualistic relationships with the human host, and it is known that our microbiota evolved together with our genome [Moran and Sloan, 2015]. However, it is also clear that microbial dysbiosis can result in disease, and the outgrowth of opportunistic pathogens can threaten the health and life of the human host.

In order to navigate and explore this exciting micro-ecosystem and its inhabitants, we need an extensive roadmap. The importance of such a roadmap is shown by the global research effort and funding dedicated to creating genetic profiles of the entire human microbiome [Mullard, 2008]. It has been suggested that the human microbiome may be thought of as the 'second human genome', and recent data published in the field have revealed that it is just as complex [Fransasiak and Scott, 2015a, 2015b]. In recent years, the microbiota in various body sites, such as the gastrointestinal (GI) and urogenital tracts, have been investigated, where it has been established that the urogenital site contributes 9% of the whole human microbiome, compared with the GI tract, which makes up 29% of the total [Peterson et al., 2009].

To understand the ever-growing metagenomic lexicon, the terminology frequently used in the field is explained in **Table 1**.

Technological advances in DNA/RNA, protein and metabolite analytic platforms, combined with the development of 'big data' computing capabilities, have revealed that the true diversity of the microbiome had been greatly underestimated, as less than 1% of bacteria grow and form colonies on agar plates [Sirota et al., 2014]. **Figure 1** depicts the multiple methods by which the microbiota of a species can be interrogated.

Profiles of the vaginal microbiome (VMB) were generated via 16S ribosomal RNA (rRNA) profiling (16S rRNA gene sequencing via PCR and pyrosequencing) [Human Microbiome Project Consortium, 2012], Sanger sequencing or via whole genome sequencing [Sirota et al.,

2014]. Recent findings from the Human Microbiome Project demonstrate that while many different species of *Lactobacillus* are present in the vaginal tract, there are a few that predominate; indeed, in comparison with the GI microbiome, the microbial diversity within the reproductive tract is relatively narrow [Gonzalez et al., 2011; Peterson et al., 2009]. These advances have transformed the field of microbial community analysis and subsequently the areas of health that may be directly or indirectly influenced by it, such as fertility and reproduction. Indeed, this transformation is shown by the exponential increase in the number of publications describing the influence of the composition and structure of the inhabiting microbial communities on reproductive health and fertility outcomes [Green et al., 2015; Haahr et al., 2016; Ma et al., 2012; Nuriel-Ohayon et al., 2016; van de Wijgert and Jaspers, 2016].

The objective of this review is to provide the reader with a clear understanding of the terminology used in this field, which is sometimes unknown to reproductive health and IVF specialists. This review will also examine the impact of a dynamic, adaptable microbiota on assisted reproductive technology procedures and reproductive outcomes, and the impact of such procedures on the composition of the microbiota itself.

The VMB of healthy women

The VMB has been recognized as an important factor involved in the protection of the host from various bacterial, fungal and viral pathogens. Moreover, the VMB of the mother plays an essential role in the initial colonization of newborn babies, which has consequences for the immune system and neurodevelopment [Dominguez-Bello et al., 2010].

A 'healthy' VMB is generally defined as a lack of symptoms and various infections, and is associated with good pregnancy outcomes. The 'normal' microbiome of the vagina in non-pregnant healthy women predominantly includes a variety of *Lactobacillus* species, which promote a healthy, supportive environment for the embryo in the pre- and peri-conceptual period [Sirota et al., 2014]. In healthy individuals, *Lactobacillus* species dominate this ecosystem at a concentration of 10^7 – 10^8 colony forming units per gram of vaginal fluid. Via the metabolism of carbohydrates and sugars, *Lactobacillus* species generate

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