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The vaginal microbiome in health and disease

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Abstract

Infections of the vaginal tract result from perturbations in the complex interactions between the microbiome and the host vaginal ecosystem. Recent data have linked specific vaginal microbes and urogenital infection with pre-term birth. Here we discuss how next generation sequencing-based approaches to study the vaginal microbiome will be important for defining what constitutes an imbalance of the microbiome and the associated host conditions that lead to subsequent infection and disease states. These studies will provide clinicians reliable diagnostic tools and treatments for women who are at increased risk for vaginal infections, preterm birth, HIV and other sexually acquired diseases, and will provide opportunities for intervention.

Microbial infections of the vaginal tract

Urogenital infections [e.g. bacterial vaginosis (BV), urinary tract infection, and vaginitis], afflict over 1 billion women each year [1-5]. These infections are associated with a large percentage of cases of vulvitis, cervicitis, and pelvic infections. BV, for example, is a complex condition thought to occur as a result of a shift in the microbial community from the normally dominant *Lactobacillus* species to a polymicrobial community, with concentrations of other aerobes and anaerobes being elevated 100- and 1000-fold, respectively [6, 7]. BV affects 10-15% of women of reproductive age and is associated with genital tract infections and pregnancy complications, including pelvic inflammatory disease, premature rupture of membranes, intrauterine growth restriction, intrauterine fetal demise, chorioamnionitis, endometritis, pre-term labor and delivery, postpartum infection, ectopic pregnancy and tubal factor infertility [8-11]. The cost of BV-related pregnancy complications in the United States alone is nearly $1 billion annually [3]. Similar statistics can be found for fungal vaginitis [12]. Approximately three out of four women experience at least one episode of vaginal candidiasis, while 20% of healthy women are asymptomatically colonized with *Candida* [13]. Recent studies have shown that the vaginal tract contains a remarkably complex microbial community and that defining a healthy vaginal environment is a considerable challenge. The emerging methods for studying the microbiome provide an opportunity to define a healthy vaginal microbiome, and link vaginal infections to a

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microbial pathogen or community structure. In this review we discuss the potential for the application of metagenomic approaches to vaginal diseases for improving women's health.

Urogenital infections and pathophysiological complications

We are just beginning to understand the interactions and relationships between the abundant, complex and dynamic microbial populations (microbiome) of the vagina and womens'health [7, 14, 15]. Despite increasing efforts and awareness, we currently know very little about how the microbiome is affected by age, menstrual cycle, genetic background or other factors in the daily lives of women, including pregnancy [16-21]. Although the final outcome of a microbial infection likely depends on many factors, the host's genetic make-up is thought to play a major role [22, 23]. For example, studies have indicated that black women are more likely to have BV than are non-Hispanic white women and that known risk factors do not explain the observed racial disparities [20, 24, 25]. Very little is known about the factors that contribute to these differences. Other metabolic processes that correlate with the presence of BV are important to consider. The malodor that is characteristic of BV has been attributed to the presence of amine-containing metabolites, and several diagnostic tests are based on the detection of these metabolites [26-34]. However, amines and amine-producing microbes have been found in asymptomatic women as well [35-41], bringing into question the association between BV and amine production and whether microbes present in a healthy vagina also produce amine-containing metabolites that may cause malodor.

In addition to the complications already discussed, urogenital infections, such a BV, are associated with the costly problem ($26.2 billion annually in societal costs), of pre-term delivery. For much of the 20th century, pre-term birth, defined as birth before 37 weeks of gestation, was viewed as an unpredictable and inevitable fact of life. About 13 million premature births occur each year, and this is a direct cause of nearly 30% of all neonatal deaths (1 million each year)[42]. In the United States prematurity ranks second for causes of infant mortality behind birth defects (Figure 1A). The world's rate of pre-term birth has also risen consistently over the past couple of decades. For example, the rate of singleton pre-term births has increased by 14% since 1990, and now accounts for 11.1% of deliveries worldwide. In 2006, pre-term births constituted 12.8% of live births in the United States, an increase of 20% since 1990, and with this there has been a corresponding increase in infant deaths related to prematurity (Figure 1B).

How is the vaginal tract microbiome associated with pre-term birth?

In most cases of pre-term labor and delivery, intrauterine infection is not clinically apparent. This may be because many hospital laboratories still use the traditional culturing methods for detecting bacterial infections [43, 44]. As uncultivated species may not be detected without the use of molecular approaches, it is possible that uncultivated vaginal species associated with preterm birth may also be discovered through analysis of the vaginal microbiome. Histologic evidence of inflammation in the decidua, fetal membranes, or umbilical cord is relatively common, and microbiologic evidence suggests that infection may contribute to approximately 25% of pre-term births, with bacterial colonization rates as high as 79% for birth at 23 weeks of gestation, declining to 11% at 31 to 34 weeks[45-47]. A recent meta-analysis study concluded that BV more than doubled the risk of preterm delivery in asymptomatic patients and of preterm labor in patients with symptoms, as well as significantly increased the risk of late miscarriages and maternal infection [48]. Moreover, there are specific associations between various vaginal microbes linked to BV (*Mycoplasma hominis*, *Gardnerella vaginalis* and *Atopobium vaginae*, alone or together) and pre-term birth [49-52]. Changes in the vaginal microbiome have also been associated with another known risk factor for pre-term delivery, shortening of the cervix in pregnancy [53]. A

conundrum exists, however, as treatment for BV has not been shown to decrease rates of pre-term delivery [54]. While some microbes can be cultured from the conceptus when suitable methods are used, pregnant women at risk for pre-term birth due to vaginal colonization with these organisms receive little or no benefit from prophylactic treatment to eradicate the organisms. The question remains, then, what is the relationship between vaginal microbes and preterm deliveries and other perturbations in the vaginal ecosystem that lead to disease states?

Understanding the vaginal tract microbiome in the metagenomic era

Our understanding of this relationship between the vaginal tract microbiome and human disease is now poised to change - A report by the National Research Council supporting a Global Metagenomics Initiative states that metagenomics "presents the greatest opportunity to revolutionize understanding of the microbial world" [55]. The term metagenomics was first used in the late 1990s, and was defined as the genomic analysis of microorganisms by direct extraction and cloning of DNA from an assemblage of microorganisms without the necessity for culturing. The availability of "next generation" sequencing technologies have made it such that a cloning step is no longer essential for metagenomic projects and one can now rapidly, and with unprecedented depth, define the total microbial community or microbiome (the number and relative abundance of microbial species present), and their metagenomes (the microbial functional content). The application of these technological advances will provide an understanding of the overall composition and physiology of the vaginal microbiome, and will provide objective analytical and biomolecular tools to assess and improve women's health. Ultimately, we believe this work will revolutionize the diagnosis and treatment of vaginal diseases, including pre-term birth, and thus will have a significant overall impact on women's health.

Metagenomics holds significant promise for increasing our understanding of many microbial diseases associated with the human body, especially those considered to be polymicrobial in origin. Indeed, the landscape of microbial ecology as it relates to human disease has been altered forever by the advent of metagenomics and has led to the National Institutes of Health's (NIH) Human Microbiome Project (HMP). The HMP has the overall goal of demonstrating the role the human microbiome plays in human health and disease by promoting a combined assessment of microbial population structure with an assessment of community function. Ultimately, the goal of the HMP is to provide a reference database of genome and metagenome sequences and an estimation of the microbial community structure at various body sites in healthy individuals. This will establish if there is a "core microbiome" at each body site indicative of a healthy status, and will provide the baseline community structure databases that will enable application of Koch's Postulates to previously intractable human diseases. That is, the correlation of microbial community structure or microbiome, rather than a single microorganism, to healthy and diseased states.

Initial studies are beginning to define the microbial, metabolic and immunologic components of the vaginal ecosystem and the effects of demographic variables on these parameters. Despite this progress, several large gaps exist in our knowledge about the vaginal ecosystem including the role of factors such as host genetics[56, 57], environmental exposure[58] and health status[59] on the abundance and interactions of individual microbial species, related taxa, and groups of distantly related microorganisms. For example, it is commonly believed that the vaginal microbiome is an indicator of health, whereas women with an altered composition of vaginal microbes are more likely to exhibit symptomatic infections and increased risk of sexually acquired diseases or pregnancy complications [60-63]. Culture-dependent identification of vaginal microbes has provided only an incomplete understanding of the vaginal microbiome [16, 64], and a profound knowledge

gap remains regarding the linkage between the vaginal microbiome and pre-term birth. For example, until recently there was a common belief that the vaginal microbiome include only a few species, predominantly from the genus *Lactobacillus*, the so-called "good" bacteria. Vaginal disease has been simplistically modeled to result from a decrease in the percentage of lactobacilli and concomitant overgrowth by other bacterial species such as *Gardnerella vaginalis*. However, it is clear from genomic analysis of *G. vaginalis[*65, 66*]* and *Lacobacillus iners[*67*]* that it is the virulence potential, both genomic and metabolic, of the strain of that is crucial, as BV isolates have numerous gene set and metabolic potentials that increase their pathogenic potential over non-BV isolates. Thus, the mere presence or absence of these bacterial species is not indicative of the disease state, but more importantly it is the metabolic potential harbored in these bacterial species that defines a commensal from a pathogenic strain.

Metagenomics and computational biology approaches are providing the biological, technological, and reference genome resources that we believe will enable significant advances in our understanding of health and disease and address the issues of metabolic potentials, not bacterial strains as indicators or mediators of disease. Whenever these techniques have been applied, whether to study environmental sites or commensal communities of humans and animals, the apparent diversity of microbes has been astounding. From the few such studies that have been conducted to survey the human vaginal microbiome, the number of species present has exceeded, by orders of magnitude, the diversity determined using classic culture-based methods [36, 38, 39, 41, 68]. Not only is there is an incredible diversity of microorganisms present within individual women, but the vaginal populations among different healthy women are highly varied [36, 38, 39, 41, 69]. Our recently published studies which showed that the vaginal microbiome is heterogeneous within an individual support this observation [70], but this is just the beginning. Although two recent studies. have examined racial differences and host genotype in vaginal microbial communities [69] [25], the impact of other variables that might contribute to microbiome composition and diversity such as age, race/ethnicity, other demographics, medications, medical conditions, sexual practices, or hormone status (normal menstrual cycle, birth control pills, menopause, pregnancy) is currently unknown. There is thus a critical need for additional high-throughput genomics based approaches to characterize the vaginal microbiome.

Concluding remarks

We believe that application of high-throughput genomic technologies to survey the bacterial, fungal, phage and viral microbiomes in combination with host genetics [71] and immunologic status, particularly as they relate to urogenital infections and pre-term birth, iskeenly needed. Such a multifaceted approach is the only way we can hope to understand how a microbiome evolves and adapts in the context of complex factors, including the host, and the varying contributions of polygenic traits on the abundance and interactions of individual microbial species, related taxa, and groups of distantly related organisms. Microbial and gene predictions (annotation and construction of genomes based on microbial reference genomes from the HMP) could be used to test the hypothesis that particular microbial taxa or gene(s) are predictors of increased risk and incidence of pre-term birth. We propose that microbial taxa or genetic markers will lead to personalized (genomic) medical diagnostics capable of being point of care predictors of risk for certain clinical outcomes that profoundly impact and improve women's health.

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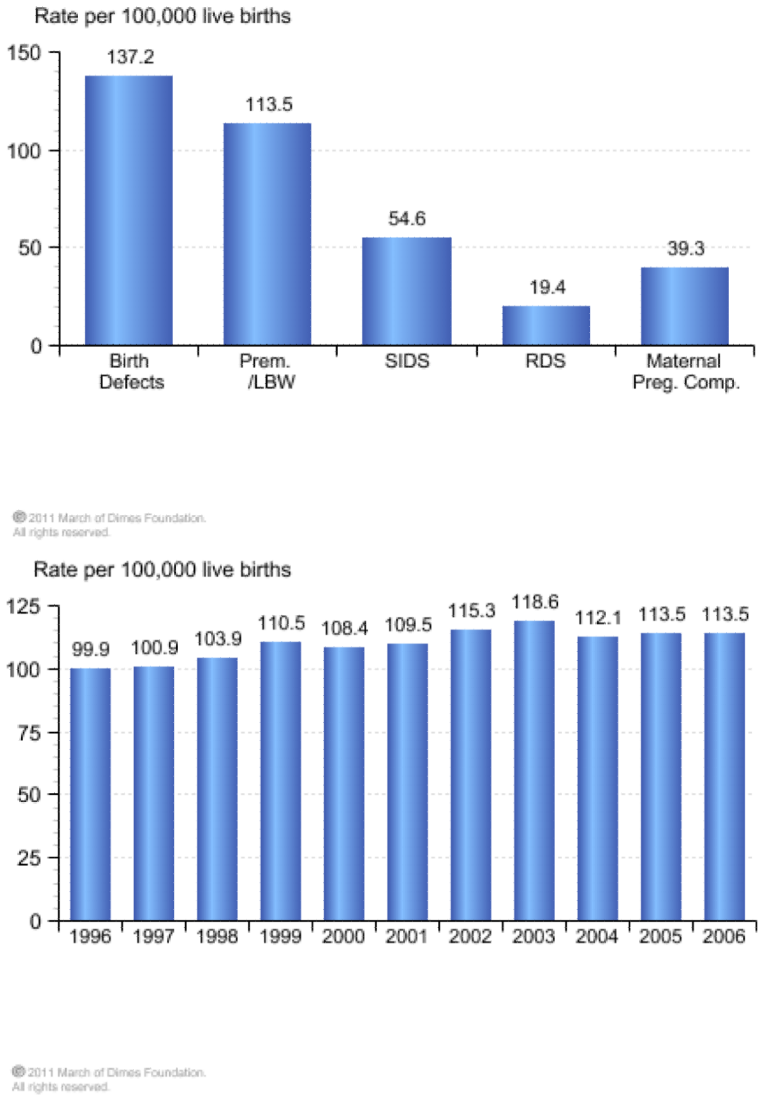

Figure.

A) Prematurity was the second leading cause of infant death in the United States in 2006 and accounted for 31.3% of all infant deaths. B) Infant deaths due to prematurity per 100,000 live births continues to be a significant problem in the United States and even increased from 1996-2006. (www.marchofdimes.com/peristats)