Pregnancy and the Vaginal Microbiome

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The vaginal microbiota is known to change throughout a woman's lifespan and for some women, pregnancy is a time when there are major alterations in her physiology with many adaptations including cardiovascular, metabolic and endocrine. Although relatively little is known about the vaginal microbiome in pregnancy, it has recently come under more intensive study; largely due to the availability of advanced techniques for characterizing microbial DNA sequences.[1-3] It has been known for years that the vagina is largely populated by *Lactobacilli* and this holds true for most pregnant women as well.

Recent studies, however, have demonstrated that pregnant women have a higher abundance of *L. vaginalis, L. crispatus, L. gasseri* and *L. jensenii*; and, the vaginal microbiota of pregnant women is more stable than that of non-pregnant women.[4-6] It is apparent, as well, that the function of the vaginal microbiome is based more on the presence of communities of bacteria as opposed to individual species. It has been proposed that there are five major community state types (CSTs) of bacteria in the vagina. Three of these are predominantly dominated by *Lactobacillus* (primarily *L. iners, L. crispatus* and *L. jensenii* or *L. gasseri*). The remaining two CSTs are characterized by a low abundance of *Lactobacillus* spp. and a predominance of Bacterial Vaginosis (BV)-associated bacteria.

Studies with relatively small sample sizes have suggested that the relative proportions of these states is different during pregnancy compared to non-pregnant women but this requires confirmation with larger numbers of women from different ethnic backgrounds, cultures and nutritional states. With a greater understanding of the normal microbial profile changes across gestation, has come an interest in understanding the variations in profiles of various pregnancy complications. In particular, our interest has been in determining the relationship between an abnormal flora and preterm birth (PTB).

It is well known that there is a 40% increase in the incidence of PTB in women who have a condition known as BV, which is characterized by a decrease in abundance of lactobacillus and an increase in organisms such as *G. vaginalis, Prevotella bivia, Mobiluncus* sp.*, Mycoplasma hominis* and *A. vaginae.*[7] The ability to sequence the vaginal microbiota of women with BV has been able to demonstrate that there are numerous bacteria present in this condition including the presence of *L. iners* in some cases.[8-10]

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Aerobic vaginitis (AE) is another condition whereby organisms such as *Escherichia coli* and *Staphylococcus aureus* dominate.[11] Both BV and AE are known to lead to an inflammatory state within the vagina and may or may not cause symptoms. In view of the relationship between BV and PTB, clinicians have attempted to treat BV during pregnancy with antibiotics which have subsequently been found to be ineffective in preventing PTB.[12] This has led ourselves and others to explore the potential utility of probiotic lactobacilli in altering the vaginal flora during pregnancy in order to prevent the onset of spontaneous PTB. Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host".[13]

The combination of the probiotic *Lactobacillus rhamnosus* GR-1 and *Lactobacillus fermentum* RC-14 has been shown to return an abnormal vaginal microbiota to normal in non-pregnant women (14). We have found that the supernatant from *L. rhamnosus* GR-1 is able to down-regulate the production of pro-inflammatory cytokines in human placental, amnion and decidual cells in vitro, and increase the production of anti-inflammatory cytokines in response to stimulation with the endotoxin Lipopolysaccharide (LPS).[15-17] It is also able to decrease significantly the rate of LPS-induced PTB in pregnant mice with a corresponding decrease in many circulating maternal and reproductive tissue concentrations of pro-inflammatory cytokines.[18]

Our recent studies in low-risk pregnant women with an abnormal vaginal flora in combination with the aforementioned in vitro and in vivo animal studies suggests that the effects of probiotics are more likely to be exerted through systemic immune responses as opposed to changing the vaginal microbiota. This is an exciting time to be investigating the role of the vaginal microbiome during pregnancy owing to the advent of the ability to determine the metabolic function of communities of microbes and their interaction with the host.[19] It is likely that there will be both local and systemic effects of these interactions which, in turn, may have differential effects on placental development and function, myometrial activity, fetal immune development and other known systemic microbial interactions.

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