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Vaginal microbes; confounders and implications on women's health

<mark>Genital microbes' role in</mark> women's health

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Abstract

The vagina has diverse vaginal microbes (Vm). A disturbance in the delicate balance maintained in Vm <mark>is</mark> linked to women's obstetrical and reproductive tract problems. Vaginal microbes play an essential role in protecting the health of the female reproductive tract by alleviating gynecological infection. However, Vm profiling has many confounders that need to be addressed during sampling, including age, race, pregnancy, medical illness, and smoking. Vm profiling improves reproduction odds, may serve as a marker for genital malignancies and have a therapeutic application in menopausal women and women with cervical cancers.

Core tips

The vaginal ecosystem has a key role in women's health. Vaginal microbes (Vm) affect the obstetrical performance of pregnant women and, in turn, can be affected by age, gestational age, race, and time of sampling. For infertile women, Vm composition can affect fertilization odds, the success of assisted reproduction technique, and even may predict the chances of live birth. The therapeutic aspect of Vm was introduced to enhance vaginal protection against infection, alleviate menopausal symptoms, and, finally, in genital malignancies. Vm was used as a signature marker in predicting and preventing ovarian and cervical malignancies, respectively.

Vaginal microbes; confounders and implication on women's health

<u>To the editor</u>

We read with interest Liao. et al.'s study published in *World J Clin Cases* that discusses the influence of vaginal microbes (Vm) on pregnant women's health and how the integrity of the vaginal ecosystem is maintained by a delicate balance of vaginal sanitation and group B streptococcus status [1].

Studying the Vm has many implications for obstetrical and gynecological diseases in women. Earlier work has examined confounders that can affect Vm, which was not discussed in Liao et al. study, including; women's age, race, pregnancy and gestational age at sampling, smoking, and sexual activity [2-4].

A recent meta-analysis described the effect of race and age on the unique ecosystem of vaginal microbes. The study confirmed that Chinese females hosted a distinct Vm from other ethnicities. In good agreement, Dunlop et al. discussed different Vm in a group of African American women vs. non-African American study population they examined [5,6].

Certain behaviors and customs can influence human races. Male circumcision, which is performed in some societies, is believed to minimize HPV transmission, a significant factor in the development of cervical cancer. Furthermore, in other communities, females may have several male partners, which may enhance the transmission of sexually transmitted diseases, including HPV[7, 8].

Other studies addressed the difference between Vm in the pregnant vs. non-pregnant population due to different hormonal influences [5].

Even for pregnant women, the sampling timing affects the observed Vm seen, as Laghi's study suggested. Moreover, they discussed the effect of females' age, diet, smoking, and sex on modifying the Vm composition [9,10].

Diseases caused by vaginal infections inversely impact obstetrical performance, like preterm labor and abortion. Furthermore, the implication of vaginal microbes on fertility outcomes and women's health in menopause was explored, given the increasing number of women entering menopause. An emphasis was made on Vm's benefit in the management of menopausal symptoms, reducing the risk of osteoporosis, regulating the nervous system, and lipid profiling for menopausal women[11-13].

Polycystic ovarian syndrome is a common cause of female infertility; research showed reduced Lactobacillus in the vagina and cervix of affected women. Consequently, fertilization rates were reduced due to oocyte damage by colonizing microbes in the oocyte's follicular fluid [14,15]. For infertile couples seeking assisted reproductive technique, an alteration in Vm and male seminal fluid microbes were linked to unsuccessful assisted reproductive technique(ART) outcome; in fact, Lactobacillus presence in the women's lower and upper genital tract favors positive outcomes[16-18].

Additionally, Vm profiling was used to predict successful in-vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) cycle and showed a predictive accuracy of 94%. Lactobacillus dominance was key in predicting pregnancy success and odds of live birth (OR 0.66, 95% CI 0.50–0.88) [19,20].

It is well known that genital infection causes a change of Vm predominant; interestingly, a correlation was found between the alteration of Vm and the development of epithelial ovarian cancer, a malignancy that is usually present in late or advanced stages. It was proposed that Vm could serve as a useful biomarker for earlier diagnosis and prevention of ovarian and cervical cancers [21-23].

Detection and clustering of Vm were based on culture-dependent methods [9,21]. However, due to their limitations, detection of Vm was shifted to culture-independent methods in the last few years, for example, Sanger sequencing of the 16S rRNA of bacterial colonies and Illumina-based amplicon sequencing of the V6 region of the 16S rRNA gene[10,21].

A therapeutic avenue of Vm was also suggested; a probiotic is a preparation containing viable microbial agents to improve health. Treatment with probiotics to relieve

genitourinary sequelae in postmenopausal women (PMW) is a promising option via restoring Lactobacillus abundance in the vagina. Recent evidence shows that oral and direct administration of probiotics in the vagina is an adjuvant therapy to estrogen withdrawal in PMW [13].

Probiotics were also used for their anticancer activities in cervical cancer via activating the maturation of natural killer cells and promoting cellular and humoral immunity. Additionally, probiotics were added to reduce the side effects of radiation therapy for cervical malignancies [25].

The COVID-19 pandemic has had a detrimental effect on fetal-maternal outcomes[26]. Celik et al. discovered a considerable change in Vm in affected cases. In fact, the more severe the maternal illness, the more Vm is altered. As a result, the researchers hypothesized that COVID-19 fosters an undesirable vaginal microenvironment. These findings point to the potential use of microbiome-associated indicators as a risk assessment tool for preterm birth in COVID-19 pregnant women. In addition, a therapeutic avenue can be created via the modification of Vm in affected cases[27].

In conclusion, Vm have confounders that need to be adjusted before sampling; moreover, Vm has implication for women's obstetrical and fertility potential. Vm can protect against infection development, be a signature biomarker for predicting ovarian cancer, and have promising therapeutic applications for PMW and patients with cervical cancer.

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