Relevance of assessing the uterine microbiota in infertility

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Technical advances in massive parallel sequencing have allowed the characterization of the whole reproductive tract microbiome in all the compartments beyond the vagina. The microbiota in the uterine cavity seem to be a continuum from the microbiota in the vagina, but several works have reported significant differences between vaginal and endometrial microbiota, highlighting the relevance of assessing the upper genital tract microbiota to better understand the potential roles of bacteria in the physiological and pathological processes taking place in the uterine cavity, including embryo implantation, pregnancy maintenance, and other gynecological diseases. However, the study of the endometrial microbiota, as with other low-biomass microbiota, presents important hurdles because, due to the small amount of starting material, they are easily contaminated by exogenous bacterial DNA. For this reason, careful and appropriate investigation of the endometrial microbiota is of outstanding importance to detect uterine dysbiosis that may impact the reproductive function. (Fertil Steril® 2018;110:337–43. ©2018 by American Society for Reproductive Medicine.)

Key Words: Endometrial microbiota, 16S rRNA sequencing, bacterial pathogens, chronic endometritis, low-biomass microbiome

The study of the female reproductive tract microbiota has been long focused on the vagina, while the presence of microorganisms in the upper genital tract (UGT) was mainly associated to infectious conditions. The first hint of endometrial colonization by commensal bacteria comes from the isolation of *Lactobacilli* along with *Enterobacter*, *Mycoplasma hominis,* and *Gardnerella vaginalis* from endometrial samples collected transcervically with a double-lumen catheter (1). Then the existence of an endometrial microbiome was further supported by the microbial growth of bacteria from uterine pieces obtained after hysterectomy, which avoids potential contamination of endometrial samples through the cervicovaginal canal in patients operated for benign conditions (2). Also using microbial culture, bacteria belonging to *Lactobacillus*, *Actinomyces*, *Bifidobacterium*, *Propionibacterium*, *Staphylococcus,* and *Streptococcus* genera have been identified in the follicular fluid. Moreover, the microbiota composition in ovarian follicular fluid shows an association with reproductive outcomes after IVF (3).

The most plausible way of UGT colonization is the ascension of microorganisms from the vagina. This hypothesis has been demonstrated by the presence of polymicrobial biofilms, containing *G. vaginalis*, attached to the endometrium and fallopian tubes of women with bacterial vaginosis (4). However, other modes of UGT seeding have been proposed, such as migration of gastrointestinal, airways, or oral bacteria via hematogenous spreading (5). These types of colonization are supported by previous findings showing similarities between oral and placental microbiomes in pregnant women (6) and the higher prevalence of cervical *Lactobacillus iners* in obese reproductive-age women in whom dysbiosis of the digestive tract is a characteristic (7). Finally, the vertical transmission of the maternal microbiome to the newborn has been suggested to influence microbial health throughout life (5).

The advent of highly sensitive molecular techniques, especially next-generation sequencing, has opened up new possibilities to explore the microbiota of body sites that were previously unexplored or considered sterile and has broadened our view of the UGT microbiota. Recently, a study has reported the microbiota across the female reproductive tract (including lower vagina, posterior fornix, cervical mucus, endometrium, fallopian tubes, and peritoneal fluid obtained from the pouch of Douglas) in women being operated for benign and noninfectious conditions (8). In addition, to confirm the viability of the bacteria found, fresh samples of peritoneal fluid, the most distal part from the vagina, were subjected to standard microbial culture, showing bacterial isolates from *Lactobacillus*, *Actinomyces,* and *Staphylococcus* genera in one third of the samples

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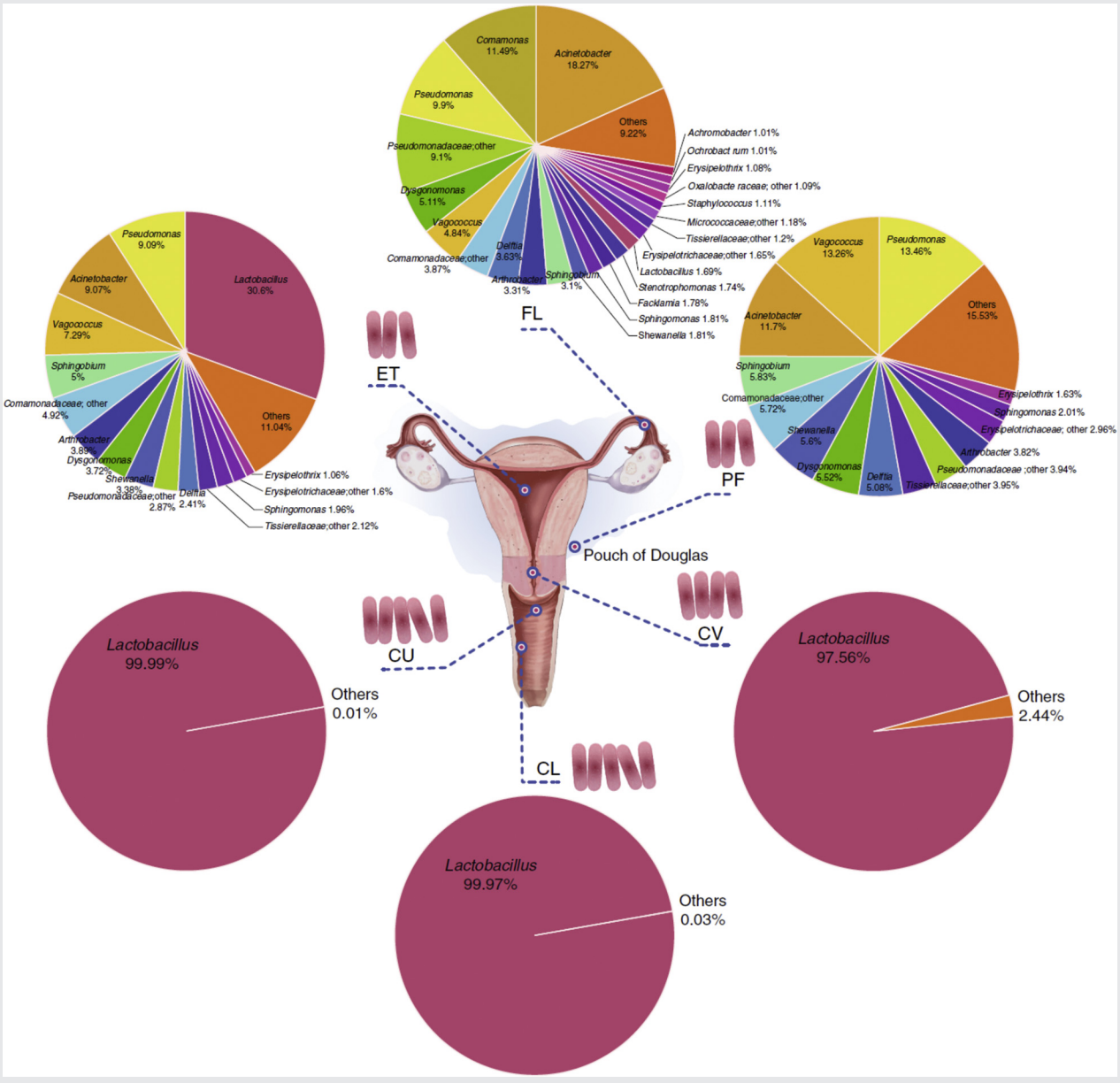
FIGURE 1



Composition of the female reproductive tract microbiota. Reprinted from Chen C, et al., The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases, *Nature Communications* 2017;8:875.

Moreno. Uterine microbiota in IVF. Fertil Steril 2018.

analyzed, confirming the existence of active bacterial microbiota throughout the UGT in reproductive age women (8). The results of this work show that there is a continuum of slightly different microbiota expanding gradually from the vagina to the ovaries (Fig. 1).

Once the existence of the whole reproductive tract microbiota is fully demonstrated, knowledge of the microbial communities inhabiting the different niches in physiological conditions will help to determine the pathological shifts that may be responsible for reproductive failure at different levels (from gamete formation in the gonads to implantation failure in the uterus and/or pregnancy complications), as well as other gynecological conditions (9, 10).

DIFFERENCES BETWEEN ENDOMETRIAL AND VAGINAL MICROBIOTA

Because embryo implantation occurs in the uterine cavity and not in the vagina, reproductive medicine remains primarily interesting in the endometrial microbiota and their impact on pregnancy establishment and maintenance.