The genital tract microbiome: bridging the gap between hype and clinical reality

O microbioma do trato genital: colmatando o fosso entre moda e realidade clínica

Pedro Vieira-Baptista[1,2]

The human mind is fueled by curiosity, by breaking barriers, by doing better and faster. Probably it is both a cause and a consequence of natural selection and, ultimately, of our evolution[1]. We "fear" the unknown, and those who succeed in understanding it acquire advantages. These advantages can be beneficial for the whole humanity (i.e., the discovery of the link between human papillomavirus and cancers[2]) or for a specific group (i.e., warfare-related inventions).

For thousands of years, we could not understand infectious diseases—before microscopy, these seemed magical events or a punishment from the gods. Leeuwenhoek was a mortal Prometheus—the steal of the knowledge of bacteria empowered humans with knowledge and paved the way for major benefits in terms of health[3].

Between the first description of *animalcules* in 1667 and the first scientific interpretations of vaginitis, we had a gap of almost two centuries. Alfred F. Donné described *Trichomonas vaginalis* in 1836, and thirteen years later, Stuart Wilkinson described a "new vegetable formation found in connection with the human uterus" (monilia) which probably were *Candida* spp. hyphae[4,5]. Half a century later, Albert Döderlein published his work on the microscopic composition of the vaginal discharge of a puerperal woman, probably never realizing the profound impact that it would have in the shaping of the way we think the vaginal microbiota, even over a century later[6]. He introduced the concept that it is normal, healthy, and desirable for women to have the vagina dominated by what he called *Lactobacillus acidophilus*. This model perfectly fits what our curious minds need to find peace: a simple and easy-to-understand model, mostly dichotomic (so much easier to classify the world as "good" or "bad," "black" or "white," "positive" or "negative" or, from a more theological perspective, as "light" or "darkness").

Curiosity could be partially soothed, but women were (are) still suffering. Only in 1955, a "new" form of vaginitis was introduced by Gardner and Dukes: *Haemophilus vaginalis* vaginitis (bacterial vaginosis)[7].

As in a road trip (or even a small commutation), one can imagine the kids in the back seat asking: "are we there yet"? And we are not…. Through the next decades, we added to the list cytolytic vaginosis, desquamative inflammatory vaginitis, and aerobic vaginitis[8,9]. But there is still so much that remains unexplained, leading women and healthcare providers to despair.

Microscopes evolved, cultures and species identification started to be part of standard practice, but knowledge progressed slowly. The turning point came with molecular techniques. With hybridization techniques and nucleic acid amplification tests (NAATs), we can easily and accurately target specific microorganisms—but we are limited to the ones we already know. They can show whether specific species or genera are present, but it still only provides a limited part of the picture (often a still picture is not enough to tell a full story). And, like with cultures, one big question remains unanswered for most microorganisms: is it causing disease/symptoms or is it mere colonization? That surely is not a problem, for instance, for *T. vaginalis*, *Chlamydia trachomatis*, or *Neisseria gonorrhoeae*—but, what about for *Candida* spp.? And, even more striking, what does an isolated identification of *Gardnerella* spp. tell us[10]?

More recently, sequencing techniques made their debut. From a single sample, you can now easily know "all" the microorganisms that populate an anatomical structure or organ. The number of papers using these methodologies from all anatomical sites is staggering. We gather more data in a couple of days than we did during the whole previous existence of mankind. Not even the remains of our ancestors are spared from our curiosity, leading us to understand events of the past and, hopefully, avoid repeating the same mistakes in the future[11].

Clearly, these techniques are part of the future, in oncology, genetics, microbiology, etc. In some cases, they clearly are already part of the clinical present.

But back to the female genital tract, do we already have the tools to adequately interpret all the data that we are gathering? Given the dynamic of the microbiome during the menstrual cycle, can we rely on the conclusions when often the samples were retrieved at different phases? And the effect of the place of sampling (i.e., is the posterior fornix equal to the anterior)[12]? Are the studies robust enough for the conclusions they draw (there is a huge pressure to show associations—but maybe we need to value more its absence than we currently do)? Can we compare different studies? And, the most important question is: are they useful in the management of patients, or for the manutention of health? From a very practical perspective, are we diagnosing better women with vaginitis?

The answer to the last question, sadly, is a very easy and straightforward one: NO! The exercise of diagnosing vaginitis remains almost universally an empiric one[13]. In despair, we see women resorting to expensive and unvalidated tests they find in the Internet (i.e., Juno, Evvy) or having NAATs to know which is their vaginal community state type (ignoring that this evolving classification never had the intention of being used for such purpose)[14]. Women enter our offices these days bringing these tests and asking for treatment based on their results. They share a common story: suffering, fear of having a sexually transmitted infection (sometimes causing stress in a relationship), fortunes spent, etc. And countless empirical treatments! In

[1]Universidade do Porto, Faculdade de Medicina, Department of Gynecology, Obstetrics and Pediatrics – Porto, Portugal. E-mail: pedrovieirabaptista@gmail.com
[2]Centro Hospitalar de São João, Lower Genital Tract Unit – Porto, Portugal.

most cases, a mere wet mount microscopy was never performed[15]. Would it be the universal answer for most cases? Certainly not, but it would have solved a large proportion of the cases[16].

Back to the concept mentioned before, of "good" and "bad"— do all women always need to have lactobacilli dominance? Certainly, it is an advantage, especially during pregnancy. But how do we correlate the concept of an "ideal" microbiome with the fact that, depending on the population, up to half of the asymptomatic women have bacterial vaginosis?

We are just starting to understand the uniqueness of the vaginal microbiome and realizing how much we really do not know. How do we fit in our mindset that the "normal" is to have dominance by a single species? It challenges all the basic rules of nature: diversity is usually good and desirable — in most other locations, dominance by one species is a state of disease; it usually means infection. Certainly, redundancy of functions within the same species can explain part of it. How and why did we evolve to be so different from all other species?

Given the huge gaps in knowledge, one must certainly question if we are ready to (try to) modulate the vaginal microbiome. The huge excitement with probiotics — for the treatment of vaginitis, for promotion of well-being, for prevention of cancers, to improve fertility, etc. It represents a huge market across the globe, despite the lack of evidence[17].

The concept of vaginal microbiome transplantation seems to be a logical answer to the inefficiency of the "simplistic" approach of using probiotics. However, it is a laborious technique, still experimental, and not 100% effective[18]. And once again, we must be careful before jumping into the conclusions, as more data are still needed before assuming it as a validated technique[19].

Other appealing and catching ideas are around, such as that of the "vaginal seeding." The concept that exposure of the fetus to the vaginal microbiome during delivery confers health benefits (asthma, atopic disease, and immune disorders) led some authors to suggest that newborns delivered by C-section should not be denied this. For that, it has been suggested that a swab containing maternal vaginal discharge should be put in the newborn's mouth. The evidence is scarce, and the procedure is not recommended by the major scientific societies[20]. The picture is, once again, highly complex: the role of breastfeeding, colonization through the skin, and the impact of hormonal changes in the weeks following delivery. The concept is appealing, but it may be contaminated by wishful thinking.

Am I preaching against investing on knowledge on the vaginal microbiome? On the contrary, we need more and better knowledge on this field. For that, we may have to be prepared to let go some of our century-old conceptions (how many studies were not published because the results did not fit the current beliefs?).

Zeus was not happy with Prometheus and, has punishment, created the first mortal woman, Pandora. Knowledge comes with a price and usually not in the form of a beautiful woman. The gods do not readily divulge their secrets and can set traps for us mortals!

Funding

The author declares no financial support.

Conflict of interest

The author declares no conflicts of interest.

REFERENCES

1. Kidd C, Hayden BY. The psychology and neuroscience of curiosity. Neuron. 2015;88(3):449-60. https://doi.org/10.1016/j.neuron.2015.09.010
2. zur Hausen H, de Villiers EM, Gissmann L. Papillomavirus infections and human genital cancer. Gynecol Oncol. 1981;12(2 Pt 2):S124-8. https://doi.org/10.1016/0090-8258(81)90067-6
3. Lane N. The unseen world: reflections on Leeuwenhoek (1677) 'Concerning little animals'. Philos Trans R Soc Lond B Biol Sci. 2015;370(1666):20140344. https://doi.org/10.1098/rstb.2014.0344
4. Donné A. Animalculi observed in purulent fluids and secretions of genital organs from Men and Women. CR Acad Sci. 1836;3(385).
5. Wilkinson JS. Some remarks upon the development of epiphytes.: with the description of a new vegetable formation found in connexion with the human uterus. The Lancet. 1849;54(1365):448-51. https://doi.org/10.1016/S0140-6736(00)63203-8
6. Döderlein A. Das scheidensekret und seine bedeutung für das puerperalfieber. Munique: Unikum; 2012.
7. Gardner HL, Dukes CD. Haemophilus vaginalis vaginitis: a newly defined specific infection previously classified non-specific vaginitis. Am J Obstet Gynecol. 1955;69(5):962-76. PMID: 14361525.
8. Cibley LJ, Cibley LJ. Cytolytic vaginosis. Am J Obstet Gynecol. 1991;165(4 Pt 2):1245-9. https://doi.org/10.1016/s0002-9378(12)90736-x
9. Gardner HL. Desquamative inflammatory vaginitis: a newly defined entity. Am J Obstet Gynecol. 1968;102(8):1102-5. https://doi.org/10.1016/0002-9378(68)90399-2
10. Stockdale CK. A positive culture result for gardnerella is not diagnostic of bacterial vaginosis. J Low Genit Tract Dis. 2016;20(4):281-2. https://doi.org/10.1097/LGT.0000000000000237
11. Khairat R, Ball M, Chang CC, Bianucci R, Nerlich AG, Trautmann M, et al. First insights into the metagenome of Egyptian mummies using next-generation sequencing. J Appl Genet. 2013;54(3):309-25. https://doi.org/10.1007/s13353-013-0145-1
12. Azevedo S, Lima-Silva J, Vieira-Baptista P. Impact of the sampling site in the result of wet mount microscopy. J Low Genit Tract Dis. 2019;23(2):176-81. https://doi.org/10.1097/LGT.0000000000000467
13. Sobel JD. Automated microscopy and pH test for diagnosis of vaginitis – the end of empiricism? NPJ Digit Med. 2023;6(1):167. https://doi.org/10.1038/s41746-023-00850-7
14. Ravel J, Gajer P, Abdo Z, Schneider GM, Koenig SS, McCulle SL, et al. Vaginal microbiome of reproductive-age women. Proc Natl Acad Sci U S A. 2011;108 Suppl 1(Suppl 1):4680-7. https://doi.org/10.1073/pnas.1002611107
15. Hillier SL, Austin M, Macio I, Meyn LA, Badway D, Beigi R. Diagnosis and treatment of vaginal discharge syndromes in community practice settings. Clin Infect Dis. 2021;72(9):1538-43. https://doi.org/10.1093/cid/ciaa260
16. Vieira-Baptista P, Stockdale CK, Sobel JD. International Society for the Study of Vulvovaginal Disease recommendations for the diagnosis and treatment of vaginitis. Lisbon: Admedic; 2023.
17. Mitra A, Gultekin M, Ellis LB, Bizzari N, Bowden S, Taumberger N, et al. Genital tract microbiota composition profiles and use of prebiotics and probiotics in gynaecological cancer prevention: review of the current evidence, the European Society of Gynaecological Oncology prevention committee statement. Lancet Microbe. 2023;S2666-5247(23)00257-4.
18. Lev-Sagie A, Goldman-Wohl D, Cohen Y, Dori-Bachash M, Leshem A, Mor U, et al. Vaginal microbiome transplantation in women with intractable bacterial vaginosis. Nat Med. 2019;25(10):1500-4. https://doi.org/10.1038/s41591-019-0600-6
19. Wrønding T, Vomstein K, Bosma EF, Mortensen B, Westh H, Heintz JE, et al. Antibiotic-free vaginal microbiota transplant with donor engraftment, dysbiosis resolution and live birth after recurrent pregnancy loss: a proof of concept case study. EClinicalMedicine. 2023;61:102070. https://doi.org/10.1016/j.eclinm.2023.102070
20. Committee Opinion No. 725: vaginal seeding. Obstet Gynecol. 2017;130(5):e274-e278. https://doi.org/10.1097/AOG.0000000000002402

Address for correspondence:
PEDRO VIEIRA-BAPTISTA
Alameda Professor Hernâni Monteiro
4200-319, Porto, Portugal
E-mail: pedrovieirabaptista@gmail.com

Submetted on: 12.28.2023
Approved on: 01.09.2024