Vulvovaginal Infections
Vulvovaginal Infections
Second Edition

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Many changes have occurred since the publication of the first edition of this book in 2007. Due to the continual development of increasingly sensitive gene amplification–based protocols, there have been major advances in the characterization of endogenous microbiota that populate the lower genital tract in women of all ages. Alterations in this microbiota in women with various vulvovaginal disorders have also been more clearly delineated. Concomitantly, there has been a large increase in our general understanding and appreciation of the different components of the innate and adaptive immune systems and their interactions. This has been paralleled by a more sophisticated appreciation of the immune mechanisms operative in the healthy female genital tract and the specific alterations that increase both susceptibility and consequences of various infectious and noninfectious disorders. Most importantly, there has been an increased appreciation of the interactions between host and microbe in the genital tract, and the importance of these interrelationships in the promotion of health or disease has been emphasized.

We are concerned that many of these recent scientific advances have not filtered down to clinical gynecologists, primary care physicians, and dermatologists with busy practices or to the residents and fellows of these disciplines. The incomplete understanding and appreciation of new knowledge in the field of vulvovaginal disorders will, unfortunately, deny their patients optimal care. A major impetus to write a second edition of this book was to try to reach busy clinicians, residents, or fellows by explaining advances in individual disorders in a manner that is relevant to their practice.

In this edition, we attempt to provide a scientific rationale for the care of patients with vulvovaginal symptomatology. To paraphrase Euclid’s counsel to Ptolemy I, there is no royal road to the care of patients with these problems. Each patient has an individual problem that often will require an investment of time and attention to assign a diagnosis properly and provide adequate and appropriate care. Our aim in this book is to provide suggestions for accurate diagnosis and care that will avoid ineffective treatments and discomfort and stress for these women.

This text offers a comprehensive approach to the subject matter. Physicians are biologists and use classification to achieve order in their patient contacts. Figure P.1, of an uncultivated forest glen, serves as an example of the lack of order in the presentation of patients with vulvovaginal symptomatology. It is an undefined picture with no clarity. In medical textbooks, this vague picture of nature’s disorder becomes transformed into the pattern of a geometrically planted nursery in which each row of seedlings and trees represents a defined clinical entity such as bacterial vaginosis, Candida vaginitis, and Trichomonas vaginitis (Figure P.2), each with prescribed symptoms, diagnostic findings, and treatment. Too often, the time-constrained physician arbitrarily assigns the patient to one of these three entities without proper testing. When the misdiagnosed patient fails to respond, she is assigned again to another of these three categories. In addition to these misclassifications, these three infectious categories do not account for all patients with vulvovaginitis. This text will expand the list of diagnostic possibilities and provide techniques to achieve a correct diagnosis and treatment options. Finally, we de-emphasize the classical signs and symptoms of various vulvovaginal disease entities. These classical presentations do not apply to the majority of patients with vulvovaginal problems, and they take attention away from the growing number of asymptomatic women who have a sexually transmitted infection. In each of the chapters on vulvovaginal disease entities, detailed treatment options are presented. Details of therapy are provided, with particular emphasis on the nuances that can be applied in women who fail to respond to the original medication prescribed or who do respond and then become symptomatic again after the treatment has ended.

Be aware of the potential limitations of our insights. Chronic vulvovaginitis has been a stepchild of medical research around the world. In many cases, the pathophysiology of disease and optimal therapy are not yet established. Each research clinic has a distinct patient population and is likely to make independent observations and establish unique practices. Opinions and practices not referenced in this text to either a specific author or to some other publications simply reflect the authors’ research clinic experience of more than three decades. Now, we invite you to read on.
FIGURE P.1 A forest glen. The disorder of nature reflects the random signs and symptoms in the diverse population of women with vulvovaginitis.

FIGURE P.2 The order of a cultivated nursery. Each row of similar plantings reflects the classifications of a vulvovaginal disease textbook in which one row represents bacterial vaginosis, another *Candida* vulvovaginitis, and the third *Trichomonas* vaginitis.
CHAPTER 1
MICROBIOLOGY OF THE VAGINA

In recent years, our knowledge of the microbiology of the vagina has undergone a profound alteration. Due to the parallel development of nonculture gene amplification techniques to amplify the bacterial gene coding for 16S ribosomal RNA and computer-generated analysis of hypervariable regions within this gene, a strikingly different and more accurate picture of the vaginal microbiome has emerged. New studies detailing the composition of the vaginal microbiome in consecutive menstrual cycles, in response to environmental changes and at different life stages, now appear frequently in the medical literature. This multitude of new data enables us to redefine what constitutes a normal, i.e., nonpathogenic, vaginal bacterial milieu and begin to more accurately evaluate and ultimately diagnose and treat individual women. However, our understanding of the mechanisms responsible for the makeup of the vaginal microbiome in individual women at different lifetime stages, and in various environments, and the triggers that induce pathological changes in bacterial composition at this site remains fragmentary. In this chapter, we will summarize the current state of knowledge of the composition of the bacterial microbiome in the lower female genital tract under different conditions and attempt to analyze the biological significance of the observations. Further analysis and interpretation of the vaginal microbiome in women with defined pathological conditions such as vulvovaginal candidiasis, bacterial vaginosis, and trichomoniasis will be found in subsequent chapters on these topics.

THE HUMAN MICROBIOME
Large multicenter and multinational government-sponsored investigations have, for the first time, begun to clearly define the intimate and mandatory relationships between the microorganisms that colonize different body sites and human physiology. It is estimated that there are 10 times more bacterial cells in our body than there are human cells, and at least 100 times more bacterial genes than human genes. Our dependence on bacterial genes for the performance of biological functions necessary for our health has been clearly elucidated. Essential nutritional, immunological, and protective roles for the endogenous commensal bacterial populations in the human gastrointestinal tract are now well established. For example, fecal transplants, in which gastrointestinal bacteria from healthy individuals are provided to people with intestinal disorders, has successfully led to a reversal of pathological symptoms. There have also been numerous attempts to alter the bacterial composition of the human vagina by the administration of purportedly “healthy” bacteria, either orally or by direct insertion into the vagina, or by altering vaginal pH with exogenous acidic preparations. Results to date have been contradictory or fragmentary due, at least in large part, to an incomplete understanding of what constitutes a normal vaginal microbiota. Before we can utilize exogenous bacteria, either natural strains or experimentally redesigned microorganisms, or other products to correct purported deficiencies and promote vaginal health, we first need to more completely understand the composition and functions of the endogenous bacteria, factors contributing to variability of the vaginal microbiome in individual women. The influence of host genetic, immune, and environmental factors on bacteria–host interactions must also be considered.

BIRTH TO PUBERTY
The prevalent dogma is that the female upper genital tract is sterile and that the newborn baby first becomes colonized with bacteria following disruption of the maternal–fetal membranes and/or during passage through the vagina. This is probably a simplistic and inaccurate view, at least for many pregnancies. Nonpregnant women may be positive for bacteria in their endometrium, and bacteria have been recovered from almost 25% of placentas
that were obtained from women who were delivered by cesarean section in the absence of labor. Bacteria, as well as viruses, have been consistently identified in amniotic fluid during the midtrimester (reviewed in Reference 5). In any event, the baby certainly becomes infected with the mother’s vaginal bacteria during delivery, and the female infant’s vagina is similar to the bacterial composition of her mother. In babies born by cesarean section to women who were not in labor, the baby’s vaginal microbiota more closely resembles the mother’s skin bacteria. In both cases, however, under the influence of the mother’s estrogen, lactic acid–producing bacteria such as Lactobacillus species colonize the vagina from the gastrointestinal tract and predominate. Estrogen promotes glycogen deposition on vaginal epithelial cells. This is degraded by host alpha-amylase and the products efficiently utilized by Lactobacilli for anaerobic glycolysis. The end product, lactic acid, renders the vagina acidic and retards or prevents the growth of other bacteria.

When the mother’s estrogen is no longer present, the vaginal pH increases toward neutrality, the female baby’s vagina loses its lactobacillus population and, instead, becomes dominated by enteric and skin bacteria as well as by Candida albicans and genital mycoplasmas. At puberty, under the influence of rising estrogen levels and renewed glycogen deposition on epithelial cells, the bacterial composition of the vagina reverts back to one dominated by lactic acid–producing bacteria.

REPRODUCTIVE AGE WOMEN

It has become abundantly clear that the vaginal bacterial population in apparently healthy reproductive age women can be quite diverse as well as changeable within one menstrual cycle or between different cycles. This has made the definition of what constitutes a normal vaginal microbiota quite difficult to pinpoint and, at the very least, clearly highlights the inaccuracy of making a clinical diagnosis on the basis of analyzing only a single vaginal sample. The following discussion highlights the predominant findings from vaginal samples obtained from women in the United States and Western Europe. Variations in predominant Lactobacillus species as well as the detection of unique bacterial genera at different frequencies might be expected in the analysis of comparable samples from women in other parts of the world and depending on economic status and cultural norms. The diversity of microorganisms most commonly present in the vagina of healthy reproductive age women is delineated in Table 1.1.

Approximately 80% of healthy reproductive age women appear to be predominantly colonized in their vagina by one or a combination of four Lactobacillus species: L. crispatus, L. iners, L. gasseri, and L. jensenii. Other lactobacillus species are also occasionally detected but are rarely predominant. In about 20% of healthy women, Lactobacilli are either present in low numbers or are undetectable, and the predominant bacterial genera may be one or a combination of facultative and anaerobic bacteria: Gardnerella vaginalis, Atopobium vaginae, Streptococcus, Prevotella, Staphylococcus, and Mobiluncus, and other biotypes. The proportion of instances in which one Lactobacillus species or bacterial genera was dominant varied with the specific population being evaluated. It is important to emphasize that other bacteria, such as Atopobium, Megasphaera, and Leptotrichia, are also lactic acid producers and, thus, an acidic vaginal pH can be maintained in the absence of Lactobacilli. The absence of a vaginal microbiota dominated by Lactobacilli is more common in Hispanic or African-American women than in women of European or Asian origin. As a consequence of this, the mean vaginal pH of healthy Hispanic or African-American women is elevated compared to that of White or Asian women.

Studies evaluating the vaginal microbiota during different stages of the menstrual cycle have yielded

<table>
<thead>
<tr>
<th>Table 1.1</th>
<th>Microorganisms most frequently detected in the vagina of healthy reproductive age women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microorganism</td>
<td>Species</td>
</tr>
<tr>
<td>Lactobacilli</td>
<td>L. crispatus, L. iners, L. gasseri, L. jensenii</td>
</tr>
<tr>
<td>Cocci</td>
<td>Staphylococcus aureus, group B and D streptococci, peptococci, peptostreptococci</td>
</tr>
<tr>
<td>Bacilli</td>
<td>Gardnerella vaginalis, Escherichia coli, Bacteroides spp., Prevotella spp., diphtheroids, propionibacteria, Clostridia spp., fusobacteria</td>
</tr>
<tr>
<td>Mycoplasmas</td>
<td>Mycoplasma hominis, Ureaplasma urealyticum, Ureaplasma parvum</td>
</tr>
<tr>
<td>Yeast</td>
<td>Candida albicans</td>
</tr>
<tr>
<td>Viruses</td>
<td>Human papillomavirus</td>
</tr>
</tbody>
</table>
highly variable results. In some women, the vaginal microbiota was stable throughout the cycle and even during menstruation, while in other women, large variations were observed at different time points. It must be emphasized that regardless of whether or not alterations in the vaginal microbiota were observed, all subjects remained in good health. Therefore, the apparent stability or instability of a woman’s bacterial population is not predictive of vaginal health. The most frequent changes in composition of the vaginal microbiota in the majority of women were observed during menstruation and following sexual intercourse. These changes were temporary. It should be noted that the microbiome of the human ejaculate has been characterized in a recent study, and there were more bacteria than there were spermatozoa in a semen sample. It has been suggested that the vaginal and seminal microbiome of sex partners may be related.12 Factors influencing the composition of the vaginal microbiota are shown in Table 1.2.

### PREGNANCY

Only a few studies have evaluated alterations in the vaginal microbiota during pregnancy,13-16 and so the data should properly be viewed as tentative and may be subject to modification. Owing most likely to the increase in estrogen, and thus glycogen deposition, during gestation, the presence of a Lactobacillus-dominated vaginal microbiota appears to increase in frequency, and non-Lactobacilli are less often detected. In addition to the lactobacillus species that predominate in nonpregnant women, one study of pregnant women found that L. johnsonii also became predominant. During the later gestational stages, the microbiome began to revert back to that present prior to conception.

Preterm birth remains the major unresolved problem in obstetrics, and ascending infection from the lower to the upper genital tract is a major cause of this event. Two studies investigated whether preterm birth could be predicted by analysis of the vaginal microbiome during pregnancy.14,16 Another investigation evaluated the vaginal microbiome in women undergoing assisted reproduction (in vitro fertilization and embryo transfer) to determine if this was predictive of outcome.17 One group observed, in women who either conceived naturally or following in vitro fertilization, that there was a greater species diversity in the microbiome of women who did not have a term birth than in women who delivered at term.14,17 They concluded that the presence in the vagina of bacteria that cannot be detected by the use of culture techniques may be important contributors to preterm delivery. However, the second study on a larger population of women concluded that the diversity and abundance of the vaginal microbiota did not differ between women who delivered preterm following preterm labor or those who delivered at term.16 Further investigations are certainly required to verify these discordant observations. A complication is that a specific bacterium may be a pathogen in one woman and a commensal in a second woman. Its relative concentration, relation to other bacteria present in the same microbiome as well as host genetic, immune, and environmental factors, will influence the likelihood of pathogenicity.

### Table 1.2 Factors influencing the composition of the vaginal microbiota

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>Promotes dominance of Lactobacilli.</td>
</tr>
<tr>
<td>Sexual activities</td>
<td>Semen, saliva, and foreign objects in the vagina alter vaginal pH and immune functions and introduce foreign microbes.</td>
</tr>
<tr>
<td>Medications</td>
<td>Alters vaginal microbiota, local immunity, and vaginal pH.</td>
</tr>
<tr>
<td>Menstruation</td>
<td>Increases vaginal pH and alters vaginal ecology.</td>
</tr>
<tr>
<td>Contraception</td>
<td>Oral contraceptives alter estrogen levels, diaphragms and condoms associated with increased enterobacteria levels, and intrauterine devices increase Bacteroides and Group B Streptococci.</td>
</tr>
<tr>
<td>Vaginal products</td>
<td>Douches, deodorants, pads, and tampons can alter vaginal ecosystem.</td>
</tr>
<tr>
<td>Immune status</td>
<td>Allergy or tolerance to specific microbes alters the magnitude and direction of local innate and acquired immunity.</td>
</tr>
<tr>
<td>Genetics</td>
<td>Individual variations in production of immune activators or inhibitors influence the capacity of the host to tolerate commensal bacteria and prevent overgrowth of pathogens.</td>
</tr>
</tbody>
</table>
VULVAR MICROBIOME
There have been only a very few published studies that have evaluated the microbiome at different regions of the vulva—labia majora, labia minora, and vaginal vestibule. In each case, the microbiota at these extravaginal locations strongly reflected the composition present in the corresponding vagina. It thus appears that bacteria present in secretions flowing from the vagina are the predominant colonizers at these external sites. It may therefore be theoretically possible to determine the predominant bacterial populations in the vagina by the noninvasive analysis of these extravaginal sites.

POSTMENOPAUSE
There is a decrease in estrogen production during menopause with the concomitant thinning of the vaginal epithelia and loss of vaginal glycogen. It is not surprising, therefore, that lactic acid–producing bacteria decline in concentration in the vagina in many postmenopausal women. This is accompanied by a rise in colonization by Gram-positive cocci, Prevotella, and coliforms and an elevation in vaginal pH. The use of hormone replacement therapy can counter this change and lead to the reinstitution of a Lactobacillus–dominated vaginal microbiota. The consequences of alteration in vaginal populations and bacterial products in women after menopause remains poorly studied.

THE UNIQUENESS OF THE HUMAN VAGINAL MICROBIOME
This chapter would be incomplete without an acknowledgement that the vaginal microbiome in women is unique and differs from that of any other species, including our primate relatives. The vaginal pH of animals most commonly used in laboratory experiments—mice, rats, and rabbits—is near neutral, and the microbiome is not dominated by Lactobacilli. Similarly, the vaginal concentration of glycogen and lactic acid, as well as Lactobacillus species, is greatly reduced in nonhuman primates as compared to women. This necessarily brings into question the relevance of nonhuman models for the study of female genital tract infections as well as noninfectious disorders. It also leads to a fascinating question that is amenable to speculation: why has the human vaginal microbiome developed its unique composition during the course of evolution and how do these alterations provide optimum protection for the human female against infection and other insults during the nonpregnant state as well as during gestation? A recent study by Stumpf et al. suggested possible explanations. The uniqueness of the human female microbiome may be due to the increased frequency of the estrus cycle compared to that of nonhuman primates, the fact that only the human female is sexually receptive at all stages of the menstrual cycle and/or that the gestational cycle in women is longer than that of other primates. In each of these scenarios, the human vagina may require unique and enhanced mechanisms of protection against infection as compared to other mammals.

LACTIC ACID
Whatever is the final explanation for the evolutionary dominance of lactic acid–producing bacteria in the human vagina, mostly lactobacillus species, it is clear that this change coincides with vaginal health. Recent studies have identified multiple mechanisms whereby lactic acid specifically promotes well-being. Lactic acid, in an acidic environment, and not other related acidic compounds, inhibits the growth of a multitude of bacteria associated with bacterial vaginosis as well as being toxic to human immunodeficiency virus. Thus, lactic acid has a unique role in promoting the dominance of microbes with a low pathogenic potential. Lactic acid is also gaining recognition as an active participant in immune defense. In the presence of a synthetic analog of double-stranded viral RNA, lactic acid was shown to specifically potentiate production of protective proinflammatory cytokines by vaginal epithelial cells. Other studies not involving the vaginal milieu have demonstrated that lactic acid promotes induction of an immune response characterized by activation of the Th17 subclass of helper T lymphocytes, promotes dendritic cells to actively present foreign antigens to lymphocytes, and induces the release of interferon gamma, a prime activator of phagocytic cells.

Lactic acid–producing bacteria are unique in their production of both the D- and L-lactic acid isomers. In contrast, mammalian cells produce L-lactic acid almost exclusively. The unique production of the D-lactic acid isomer by some strains of Lactobacilli may enhance protection against microbial invasion of the upper genital tract. Matrix metalloproteinase (MMP)-8 is known to alter the integrity of the cervix. The inducer of MMP-8, extracellular matrix metalloproteinase inducer (EMMPRIN), is produced by vaginal epithelial cells, and its concentration in vaginal secretions is dependent upon the relative levels of D- and L-lactic acid. High D-lactic acid production limits EMMPRIN concentrations, and thus MMP-8 levels and minimizes MMP-8–induced cervical changes that can promote bacterial migration to the upper genital tract. Interestingly, L. iners differs from L. crispatus, L. gasseri, and L. inersii by its inability to produce D-lactic acid. L. iners, at least the one strain that was evaluated, was shown to lack
the gene coding for d-lactate dehydrogenase. The clinical implications of this observation remain to be determined. However, several studies have indicated that L. iners is often associated with the presence of atypical vaginal bacteria as well as the presence of clinical symptoms. Further investigations to explore the relationship between d-lactic acid and vaginal health are warranted.

SUMMARY AND CONCLUSIONS
It is now abundantly clear, based primarily on development and refinements in nonculture methods of bacterial identification, that there is not one single human vaginal microbiome that defines what is normal. Instead, multiple microorganisms are consistent with normality. Furthermore, a relatively constant vaginal bacterial composition or one that fluctuates during or between menstrual cycles is both equally associated with a healthy vagina, i.e., the absence of physical symptoms. Studies that have evaluated the vaginal microbiota at only a single time point and correlated the findings with various disorders may, thus, be erroneous in their conclusions. To label as abnormal vaginal populations in asymptomatic women that are not dominated by Lactobacilli and treat these women with antibiotics or other antimicrobial preparations may very well be ill advised. This may merely interfere with the woman’s unique vaginal ecosystem and increase her susceptibility to growth of microorganisms that are normally suppressed. It is incumbent upon the practitioner to first determine what is normal for each individual patient before initiating a course of treatment to alter her vaginal microbiomal environment. Further analysis of the vaginal microbiome and the presence of unique microbial metabolites in the vagina may lead to development of nonantibiotic-based treatments for the prevention of infection-related preterm birth, especially in resource-poor area of the world.

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Vulvovaginal Infections


Microbiology of the Vagina


Vaginal Immunology


Diagnosis of Vulvovaginal Disease


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Human Papillomavirus Genital Infections


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