Published in final edited form as:
Semin Fetal Neonatal Med. 2012 February ; 17(1): 51–57. doi:10.1016/j.siny.2011.08.006.

Microbiota of the upper and lower genital tract

Ryan Rampersaud[a], **Tara M. Randis**[b], and **Adam J. Ratner**[a,b,*]

[a]Department of Microbiology & Immunology, Columbia University, New York, New York, USA

[b]Department of Pediatrics, Columbia University, New York, New York, USA

Summary

Our understanding of the bacterial species inhabiting the female genital tract has been limited primarily by our ability to detect them. Early investigations using microscopy and culture-based techniques identified lactobacilli as the predominant members of the vaginal microbiota and suggested that these organisms might serve a protective function at the mucosal surface. Improvements in cultivation techniques and the development of molecular-based detection strategies validated these early findings and enabled us to recognize that the microbiota of the female genital tract is much more complex than previously suspected. Disruption of the vaginal microbial community due to invasion of exogenous organisms or by overgrowth of one or more endogenous species has important health implications for both the mother and newborn.

Keywords

Bacterial vaginosis; Lactobacilli; Vaginal microbiota; Vaginitis

Introduction

The microbial inhabitants of the female genital tract and the contribution of these organisms to health and disease have been investigated for well over a century, yet they remain incompletely understood. The earliest studies focused on the microbiology of the lower genital tract and relied upon growth of bacteria in rich medium and identification based on observable characteristics (including shape, Gram stain, and arrangement of cells). These investigations led to important insights including the identification of lactobacilli as the predominant members of the vaginal ecosystem in most women, to the hypothesis that these organisms might serve protective functions at the vaginal mucosal surface, and to the presumption that the upper genital tract is sterile under normal conditions. With advances in bacteriological culture strategies, scientific understanding of the vaginal microbiota became significantly more nuanced. However, only a fraction of microbes can be cultured in the laboratory even with the most modern techniques, limiting studies of the host-associated microbiota. As culture-independent measures of microbial diversity have been developed and used, the microbiota of the vagina and upper genital tract have been revealed as

*Corresponding author. Address: Columbia University, 650 West 168th Street (BB 443), New York, NY 10032, USA. Tel.: +1 (212) 342-2902; fax: +1 (212) 342-5218. ar127@columbia.edu (A.J. Ratner)..

Conflict of interest statement None declared.

considerably more dynamic and complex than previously suspected, with important implications for the health of women and infants.

Normal microbiota

Lower genital tract

The earliest debates about the relevance and even the existence of bacterial inhabitants of the female genital tract date to the 1870s and reached a quite contentious point by the turn of the century (reviewed by Williams[1]). The primary question under investigation at that time was whether puerperal sepsis resulted from external contamination of normally sterile sites (e.g. by the hands of physicians or midwives) or whether the necessary etiologic agents existed in the vagina or uterus under normal circumstances. In 1887, Gönner[2] and Döderlein[3] separately examined this issue and came to opposite conclusions. Gönner noted a failure to culture pyogenic organisms (staphylococci, streptococci) from the vaginal secretions of pregnant women (and, presciently, observed that on direct examination of coverslip preparations there were a multitude of visible organisms that did not grow in subsequent culture). By contrast, Döderlein found carefully obtained uterine samples to be sterile but vaginal secretions frequently to contain pyogenic cocci, placing him firmly in the camp of `autoinfectionists' (these early studies are reviewed by Williams[1]). In 1892, Döderlein published a monograph, *Das Scheidensekret* (`vaginal secretions'), reporting the bacteriological investigation of nearly 200 pregnant women.[4] This work provided further evidence supporting his autoinfectionist viewpoint but more importantly contained the first descriptions and images of the vaginal bacillus, subsequently called the Döderlein bacillus (later *Lactobacillus acidophilus*[5]).

Döderlein divided the bacterial communities of pregnant women into normal (dominated by the vaginal bacillus) and abnormal (containing numerous other organisms, frequently streptococci or staphylococci). He argued that in the normal secretions, conditions promoted by vaginal bacilli, including acidity, were crucial to keeping the vagina free of pathogenic bacteria.[4] This was a crucial concept, one that continues to inform investigations into vaginal microbial ecology. Understanding the mechanisms by which vaginal lactobacilli protect from colonization or infection by other organisms (colonization resistance or bacterial interference) is a longstanding goal. Thomas noted the absence of lactobacilli in vaginal samples from women with gonorrhea and attempted to use instillation of cultures of lactobacilli as therapy as early as the 1920s.[5] Subsequent studies also described an inverse relationship between lactobacilli and *Neisseria gonorrheae* in the vagina, suggesting antagonism.[6] Further study attributed the protective effects of vaginal lactobacilli to several mechanisms including the production of hydrogen peroxide and lactic acid (which maintains the vaginal tract at an acidic pH) the production of bacteriocins (small peptides with microbicidal activity) and competition for nutrients or receptors at the epithelial surface (reviewed by Reid et al.[7]). The relative importance of each of these mechanisms remains unclear.[8]

Subsequent improvements in culture techniques and in biochemical characterization of micro-organisms have led to important additional insights: that the `Döderlein bacillus' is not a single organism but a heterogeneous group of lactobacilli with distinct characteristics[9–11] and that the vaginal microbiota is composed of considerably more than a simple monoculture of lactobacilli. The readily cultivable vaginal lactobacilli are now divided into a small number of dominant species, chiefly *Lactobacillus crispatus*, *Lactobacillus jensenii*, and *Lactobacillus gasseri*.[12] Studies from the 1970s until the advent of culture-independent techniques greatly expanded the census of vaginal microbes. The use of quantitative culture, improved transport media, and anaerobic incubation particularly drove this expansion (reviewed by Larsen and Monif[13]). Among the aerobes and facultative

organisms, lactobacilli, other Gram-positive rods, staphylococci and streptococci (of both pathogenic and non-pathogenic varieties), and Gram-negative enteric organisms can all be found at high prevalence in vaginal samples. Likewise, a variety of cultivable anaerobes including *Prevotella* spp., *Fusobacteria* spp., and others are present in substantial numbers at the vaginal mucosal surface.[13]

It has been clear since at least the days of Gönner that culture-based investigations of the vaginal microbiota are intrinsically limited. Cultivation-independent techniques bypass the need to grow microbes in culture and rely instead upon isolation of DNA from a given sample followed by techniques to identify individual microbial community members. The bacterial 16S rRNA gene is most commonly used as a means of identification, because it is highly conserved among species but possesses several hypervariable regions that can allow identification to the genus or species level (reviewed by Clarridge[14]). Briefly, primers are generated to the conserved regions of the 16S rRNA gene, producing a polymerase chain reaction (PCR) product that spans one or more of these hypervariable regions. These products can then be analyzed in several ways to assess community structure. These methods include terminal restriction fragment length polymorphism (T-RFLP) analysis, in which PCR products are generated and digested with restriction enzymes, yielding patterns of fragments used for identification. The PCR products may also be analyzed by denaturing gradient gel electrophoresis (DGGE) in which they are separated based on sequence differences by subjecting them to the activity of a gradient of denaturing chemicals. Whereas T-RFLP and DGGE are useful and economical techniques, direct sequencing of 16S PCR products yields the most detailed information and, as sequencing costs have decreased, has become the most commonly used technique. The recent transition from low-throughput clone library sequencing studies to deep sequencing of PCR amplicons has led to a rapid accumulation of data regarding human-associated microbial communities and has been crucial in furthering our understanding of the microbiota of the genital tract.

16S-based studies have largely confirmed the broad conclusion of Döderlein, that lactobacilli are the dominant organisms in the vaginal tract of most healthy premenopausal women, but they have also refined that view significantly. For example, an early culture-independent investigation seemed to confirm *L. crispatus*, *L. jensenii*, and *L. gasseri* as the most numerous members of the vaginal lactobacilli.[12] However, 16S-based studies have also revealed a major role for a more recently identified organism, *Lactobacillus iners*, which had been largely overlooked in early investigations because of its fastidious growth requirements[15] likely due to significant genome reduction.[16] In a 2002 study, *L. iners* was found to be a frequent constituent of the vaginal microbiota of Swedish women,[17] and Burton et al. subsequently found *L. iners* to be the most frequently detected vaginal lactobacillus in their sample of premenopausal women.[18] Individual differences in *Lactobacillus* spp. composition of the vaginal tract between women of different geographic locations, races and ethnicities have been noted across multiple studies.[19,20]

Most of these early culture-independent studies relied on T-RFLP/DGGE with targeted sequencing of some PCR products and thus were limited in resolution. A 16S clone-and-sequence approach was used by Hyman et al. to investigate the vaginal microbiota of healthy women and by Fredricks et al. to study women with and without bacterial vaginosis.[21,22] These studies were largely limited to genus-level identification of microbes, but they provided a glimpse of the vast, unappreciated diversity of uncultivated and lower-abundance bacteria present at the vaginal mucosal surface. The most detailed investigation to date used deep sequencing of 16S PCR products to probe the vaginal microbiota in 396 women of childbearing age.[23] Despite considerable inter-individual diversity, the microbial communities clustered into five groups, four of which had a single dominant *Lactobacillus* sp., and one `diversity group', the members of which did not have a lactobacillus-dominant

microbiota. It is notable that the *L. iners*-dominant group was the most common among the five, though this was not true across all racial and ethnic groups. Hummelen et al. used deep sequencing of 16S amplicons in a cohort of human immunodeficiency virus (HIV)-positive women in Tanzania and described *L. iners* and *Gardnerella vaginalis* as members of a core microbiota (i.e. present in all samples tested).[24]

Follow-up of these deep sequencing approaches with targeted PCR or microarray-based detection of specific organisms has provided tools to examine short term fluctuations in the vaginal microbiota. Daily sampling with PCR-based quantification of vaginal bacterial species in a small sample of women demonstrated substantial variability in individuals over very short time periods as well as significant shifts in species composition associated with menses.[25] Factors influencing the normal vaginal microbiota may include age, hormonal status/phase of menstrual cycle, host genetic background, exposure to sexually transmitted agents, immune status, and possibly diet and nutritional status.[26] Long-term studies with frequent sampling will be needed in order to gain a better understanding of the factors driving the diversity and the dynamics of the vaginal bacterial community.

Upper genital tract

Despite the extensive microbial colonization of the cervico-vaginal epithelium, the tissues of the upper genital tract are generally considered to be sterile.[27] Introduction of bacteria into these tissues is typically associated with identifiable disease (endometritis or pelvic inflammatory disease[28,29]). However, the results of several culture-based based investigations documenting recovery of organisms from the endometrium of healthy, asymptomatic women challenge this notion of sterility.[30–32] Contamination with bacteria from the lower genital tract, particularly when using a transcervical technique for specimen collection, is one potential explanation for these findings.[33] However, endometrial cultures obtained via surgical hysterotomy in women presenting for hysterectomy have yielded similar results. Specimens obtained using this intraoperative technique indicate that ~25–30% of subjects harbor one or more micro-organisms in the uterus, with *Lactobacillus* spp., *Mycoplasma hominis*, *Gardnerella vaginalis* and *Enterobacter* spp. the most frequently recovered.[34,35]

Additional evidence in support of a non-sterile intrauterine environment comes from studies demonstrating the ability of some bacteria to attach to human spermatozoa, enabling transport through the cervix and into the intrauterine space.[36] Despite these data, bacterial colonization of the upper genital tract of healthy, asymptomatic women remains a somewhat controversial issue.

During pregnancy, the placenta, fetal membranes, and cervical mucus plug function collectively to defend the developing fetus from invading organisms. Several adverse obstetric outcomes including miscarriage,[37] chorioamnionitis,[38,39] premature rupture of membranes (PROM)[40] and preterm birth[41] have been associated with presence of bacteria in the intrauterine cavity. These sequelae are believed to be the direct result of the maternal and sometimes fetal inflammatory response to bacterial pathogens.

It is difficult to ascertain whether bacteria may exist in these tissues without inducing a deleterious inflammatory response (i.e. colonization without infection). Because rupture of the fetal membranes[40] and uterine contractions[42] are independently associated with microbial invasion of the intrauterine cavity, only studies using specimens obtained from women with intact membranes, prior to the onset of labor, can adequately address this question. Therefore, the majority of investigations are made in women delivering preterm secondary to maternal indications, such as pre-eclampsia, or in those presenting for elective cesarean section at term gestation. Variability in the specimen collected (placental tissues

versus fetal membranes or amniotic fluid) and methodologies employed for bacterial detection (culture-dependent versus molecular-based techniques) contribute to the difficulty in interpreting reported data.

Onderdonk et al. used culture-based techniques to examine placental biopsy specimens obtained from women delivering in the second trimester of pregnancy.[43] Bacteria were recovered in nearly 25% of placentas delivered via cesarean section in the absence of labor with intact fetal membranes, leading the authors to conclude that the presence of organisms in these tissues represented colonization as opposed to infection. They further speculated that in some cases, colonization of the placenta may be beneficial, promoting normal development of the fetal immune system without harm to fetus or mother. Steel et al. used in-situ hybridization to detect bacterial RNA in fetal membranes and demonstrated that preterm tissues delivered by cesarean section in the absence of labor with intact membranes contain bacteria as frequently as those collected after preterm labor or PPROM (nearly 85% of samples).[44] These investigators concluded that the presence of bacteria in these tissues is not necessarily sufficient to induce inflammation and subsequent preterm labor. Whether these pregnancies would have continued to term is unknown. Interestingly, this same study revealed that the 70% of tissues delivered by elective cesarean section at term in the absence of labor were positive for the presence of bacterial RNA.[44] By comparison, the frequency of microbial invasion of the amniotic cavity was noted to be only 1% in a similar cohort of women when standard culture techniques were used to examine the amniotic fluid specimens. This finding may represent the presence of dead microbes or the limitations of culture-based study.

Disturbances of the genital tract microbiota

Disruption of the vaginal microbial community may occur following invasion of an exogenous organism, as is the case with monoetiologic diseases such as gonorrhea or chlamydia, or by overgrowth of one or more endogenous commensal species, as occurs in bacterial vaginosis or aerobic vaginitis. This later mechanism is particularly problematic with regards to defining disease, identifying causative agents and distinguishing colonization from infection. Several of these issues are highlighted below.

Bacterial vaginosis

Bacterial vaginosis (BV) is a condition characterized by replacement of the normally protective *Lactobacillus* spp. with a massive overgrowth of anaerobic and facultative organisms including *Gardnerella vaginalis, Atopobium vaginae, Bacteroides* spp., *Mobiluncus* spp., and genital mycoplasmas.[45,46] This alteration in vaginal microbiology may lead to symptomatic vaginitis. However, the vast majority of affected women remain asymptomatic.[47] Regardless of clinical presentation, BV is associated with significant adverse consequences including miscarriage,[48] preterm birth,[49] chorioamnionitis,[50] postpartum endometritis[51] and an increased risk of HIV acquisition.[52] This complex disorder is exceedingly common, with prevalence rates ranging from 10% to 40%.[53] Suboptimal methods of diagnosis reflect the inherent difficulties in precisely defining this condition and make the true prevalence difficult to ascertain.

In 1955, Gardner and Dukes isolated *Haemophilus vaginalis*, now known as *G. vaginalis*, from women with `nonspecific vaginitis' and postulated that this was the primary etiological agent.[54] Their attempts to induce infection in healthy volunteers by inoculating pure cultures *of G. vaginalis* were largely unsuccessful (only one of 13 volunteers infected).[55] They were, however, able to induce vaginitis in 11 of 15 volunteers by inoculating vaginal secretions from affected women, suggesting that *G. vaginalis* alone was not sufficient to induce disease and that additional factors/organisms were necessary. Since that time, numerous BV-

associated bacteria have been identified using both standard culture and cultivation-independent techniques and BV is generally regarded as a polymicrobial disease. Nevertheless, *G. vaginalis* remains one of the most frequently isolated organisms in women with BV[56] and its cytotoxicity and ability to produce an adherent biofilm suggests a greater virulence potential relative to other BV-associated organisms.[57–59]

Because of the failure to define a single causative infectious agent and because most BV-associated bacteria may be found in women without disease, the utility of standard culture for diagnosis is limited. Hillier et al. noted that the positive predictive value of a positive *G. vaginalis* culture is <50%.[45] Amsel's criteria, although widely accepted as the best available means to diagnose BV in the clinical setting[60] may fail to identify women with asymptomatic BV. Alternatively, BV may be diagnosed using the Nugent scoring system for interpretation of Gram-stained vaginal smears. This method assesses the number of lactobacilli relative to BV-associated bacterial morphotypes in order to characterize vaginal microbiota as normal, intermediate or abnormal (BV).[61] A major criticism of this diagnostic strategy is that although women with high numbers of *Lactobacillus* spp. generally do not have BV, it may be incorrect to conclude that women with few or no *Lactobacillus* spp. have BV.[62] In the study by Ravel et al. described above, nearly 25% of asymptomatic reproductive-age women had vaginal bacterial communities in the `diversity group' (i.e. not dominated by *Lactobacillus* spp.).[23] In addition, questions regarding the risk of potential morbidities and the need for antimicrobial therapy in those women found to have `intermediate flora' remain unanswered.[63]

The use of cultivation-independent techniques has not only enhanced our understanding of the microbiology of BV but has also recently been explored as a potential diagnostic strategy. Fredricks et al. used 16S rDNA PCR to characterize and compare the bacterial communities found in women with and without BV.[21] They demonstrated that those subjects with BV exhibited considerably greater bacterial diversity, with 35 bacterial phylotypes detected, 16 of which were newly recognized. By contrast, women without BV were noted to have relatively homogeneous vaginal microbiota, predominantly comprised of lactobacilli. Preliminary studies using targeted (taxon-directed) broad-range assays to detect these novel species reveal a diagnostic performance comparable to that of the Amsel or Nugent criteria.[64] Application of these molecular-based techniques to detect organisms traditionally associated with BV may also be of benefit. Real-time PCR analyses of vaginal specimens indicate that increased concentrations of both *G. vaginalis* and *A. vaginae* are highly specific for BV.[56] A prospective study examining the diagnostic accuracy of quantitative PCR assay for these two organisms found this strategy to have a high sensitivity (100%) and specificity (93%) in relation to standard methods of diagnosis.[65] Although these culture-independent methodologies exhibit promise as potential diagnostic modalities, the prohibitive cost, necessary equipment and required technical expertise preclude their routine use at this time.

The physiologic mechanisms by which BV leads to adverse pregnancy outcomes remain poorly understood. It is possible that replacement of the lactobacillus-dominated microbial community with an overgrowth of BV-associated organisms stimulates a local or systemic inflammatory response that ultimately reaches the intrauterine environment. This explanation is somewhat unlikely as BV is characterized by a paucity of infiltrating immune cells, and, although increases in local cytokine concentrations have been documented, circulating levels of serum cytokines remain unchanged.[63,66] Alternatively, these adverse outcomes may be attributable to the ascension of BV-associated bacteria into the intrauterine space.[50,67] Evidence in support of this hypothesis is presented below.

Aerobic vaginitis

Recently, a second major abnormality of the vaginal microbiota, termed aerobic vaginitis (AV), has been described. In this disorder, the normally present *Lactobacillus* C spp. are replaced with aerobic organisms, predominantly enteric commensals or pathogens.[68] Such a community was most often classified as `intermediate' in previous investigations. Donders et al. proposed the following microscopic features to diagnose this disorder: (1) a paucity of lactobacilli; (2) an increased number of leukocytes; (3) the presence of parabasal cells (a sign of epithelial inflammation); and (4) the presence of cocci or coliform bacteria.[69] By contrast with BV, women with AV exhibit a robust immune response, with markedly elevated vaginal concentrations of interleukin (IL)-1b, IL-6, IL-8 and leukemia inhibitory factor. Furthermore, this condition produces clinical signs and symptoms of vaginitis in >70% of those affected.

Group B streptococci (GBS), *Escherichia coli*, and *Staphylococcus aureus* are the organisms most frequently associated with AV.[69] Of note, 20% of women with AV also exhibited an overgrowth of *G. vaginalis*, indicating that there may be a degree of overlap with BV or that the two entities may coexist.[69] Prospective analyses have linked AV with several pregnancy-related complications including late miscarriage, chorioamnionitis, and preterm birth.[68,70,71] The precise role of AV during pregnancy, the utility of screening, and potential therapies require further study.

Ascending infection and chorioamnionitis

Chorioamnionitis refers to inflammation of the fetal membranes and placental chorion most typically due to an ascending bacterial infection. It is believed that vaginal organisms first invade the choriodecidual space (between the maternal tissues and the fetal membranes) and then infect the amniotic fluid by crossing intact chorioamniotic membranes.[72] Less frequently, organisms may gain access to these tissues via migration from the abdominal cavity through the Fallopian tubes, iatrogenic inoculation during amniocentesis or chorionic villus sampling, or hematogenous spread from distant sites.[72,73] The presence of microbes in the chorioamnion generates a maternal and, in some cases, a fetal inflammatory response characterized by the release of proinflammatory cytokines and chemokines[39] that may lead to cervical ripening, membrane injury, labor at term or premature birth at earlier gestational ages.[74] Because the vast majority of intrauterine infections are subclinical, identifying women with chorioamnionitis poses a major challenge.

In women in spontaneous preterm labor with intact membranes, the most commonly identified bacteria in the amniotic fluid using standard culture techniques are *Ureaplasma urealyticum* (47%) and *Mycoplasma hominis* (30%), *G. vaginalis*, *Bacteroides* spp. and peptostreptococci.[67,72,75,76] Group B streptococci and *Escherichia coli* are most often isolated in clinically symptomatic women and may associated with aerobic vaginitis [68,71] Chorioamnionitis secondary to *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, though infrequent, has also been described, particularly after membranes have ruptured.[72,77] Chorioamnionitis is typically a polymicrobial infection, with >65% of positive amniotic fluid cultures growing two or more organisms.[74] In some instances, intra-amniotic inflammation is detected although bacterial cultures remain sterile. This likely reflects infection with uncultivated species.

DiGiulio et al. used both standard culture and broad-range PCR to analyze the amniotic fluid of women in spontaneous preterm labor with intact membranes.[78] They demonstrated that the microbial prevalence in the amniotic fluid using this method was 56% higher than that found by routine cultivation methods. Species detected by PCR alone included *Streptococcus mitis*, an uncultivated *Bacteroidetes* bacterium, Delftia acidovorans, Neisseria

cinerea, sneathia sanguinegens, Leptotrichia amnionii and one previously uncharacterized bacterial species. These investigators highlighted the clinical relevance of these findings by demonstrating that a positive PCR result had a 100% positive predictive value for preterm delivery in this cohort.

The use of broad-range PCR to identify bacterial DNA in the amniotic fluid has increased our understanding of the diversity and abundance of microbial species invading the amniotic cavity in the setting of preterm labor. Importantly, this methodology may allow for more timely intervention and appropriate antibiotic selection.

The vaginal microbiota as a reservoir for neonatal pathogens

Bacterial communities that exist in the lower genital tract are among the first to colonize the neonate following vaginal delivery and therefore contribute to the establishment of the skin and intestinal microbiota of early infancy.[79] A number of well-recognized neonatal pathogens may be found in the vaginal tissues of healthy pregnant women and the vertical transmission of such organisms is associated with increased risk for invasive bacterial disease in the early neonatal period.

Group B streptococcus—Group B streptococcus (GBS) is a leading infectious cause of morbidity and mortality among neonates, and colonization of the maternal genital tract, occurring in 20–25% of pregnant women, is the primary risk factor for neonatal disease.[80,81] The gastrointestinal tract is believed to be the primary human reservoir for group B streptococcus and the likely source of vaginal colonization in pregnant women.[82] Vaginal colonization may be transient, intermittent or chronic.[83] Epidemiologic studies suggest that black race, multiple sexual partners, increased maternal age, previous spontaneous abortion, increased sexual activity, and altered vaginal bacterial communities (decreased *Lactobacillus* spp. and concurrent colonization with *CCandida* spp.) are risk factors for vaginal colonization with GBS.[84–86]

Vertical transmission of GBS to the neonate occurs in ~50% of colonized mothers. Of those colonized infants, 2% will go on to develop early onset GBS infection (reviewed by Baker[87]). Transmission to the fetus or newborn occurs through direct exposure during passage of the infant through the birth canal or via ascension of the organism from the vagina to the intrauterine space. Efforts to prevent vertical transmission of GBS, including universal maternal screening and antepartum antibiotic prophylaxis, have led to a nearly 80% reduction in the incidence of early onset disease.[88]

Gram-negative enteric organisms—Gram-negative bacteria that typically inhabit the gastrointestinal tract may also colonize vaginal mucosal surfaces. These organisms may be transmitted to the fetus or newborn during the perinatal period and are associated with substantial neonatal morbidity. *Escherichia coli* most prevalent of these and is responsible for the majority of cases of early onset sepsis in preterm infants, and is the most frequent cause of early onset meningitis.[89] A recent prospective study designed to identify primary determinants of mucosal colonization of newborns in the neonatal intensive care unit revealed that vaginal delivery was associated with a fourfold higher risk of colonization by *E. coli*, indicating that these organisms are likely of maternal origin.[90]*E. coli* strains possessing the K1 capsular antigen exhibit a specific tropism for the central nervous system and are responsible for ~75–80% of neonatal cases of *E. coli* meningitis.[91] Culture-based studies demonstrate *E. coli* K1 vaginal colonization rates ranging from 5% to 7% throughout pregnancy.[92] Vertical transmission of the K1 serotype from mother to infant is exceedingly common, with 50% of infants colonized if their mothers were positive for this organism at the time of delivery.[93] Other Gram-negative pathogens including *Haemophilus, Klebsiella,*

and *Enterobacter* spp. have been isolated from the maternal genital tract and are less frequent, but have been reported as causes of neonatal early onset sepsis.[89,94,95]

Staphylococcus aureus—Most newborns are colonized with *Staphylococcus aureus* within the first few days of life.[96] The vast majority of infants acquire *S. aureus* through direct contact with the skin of caretakers and healthcare personnel. However, the maternal vaginal tract has become an increasingly recognized source of neonatal colonization. A recent epidemiologic study indicated that *S. aureus* colonization rates in newborns are tenfold higher when the mother is a vaginal carrier than when she is not.[97] Furthermore, among maternal carriers, delivery by caesarean section significantly decreases the likelihood of *S. aureus* colonization in the neonate compared to vaginal delivery. Of concern is the increasing proportion of neonates harboring meticillin-resistant *S. aureus* (MRSA). A large, single center, prospective surveillance study revealed that 3.5% of infants admitted to the neonatal intensive care unit between 1993 and 2006 were colonized with MRSA.[98] Vaginal delivery was again noted to be an independent predictor for neonatal colonization.

The estimated prevalence of vaginal colonization with *S. aureus* during pregnancy ranges from 14% to 21%.[98–100] Both meticilli-susceptible *S. aureus* and MRSA colonization are significantly more common among GBS-positive than GBS-negative women.[99] Vaginal colonization with *S. aureus* is often asymptomatic, except when associated with AV.[69] Although the attack rates for infection following neonatal colonization are low, *S. aureus* remains an important neonatal pathogen, particularly in the intensive care setting.

***Ureaplasma* species—**Vaginal colonization with *Ureaplasma* spp. occurs in 40–80% of women.[101] Transmission to the fetus may occur following ascending infection or hematogenous spread through the placenta and umbilical vessels.[102] Alternatively, the neonate may acquire the organism during passage through the birth canal with subsequent colonization of the skin, mucosal membranes and respiratory tract.[101] Vertical transmission appears to vary according to gestational age. One prospective study revealed a vertical transmission rate of 60% for newborns weighing ≤1000 g vs only 15.3% for infants weighing ≥1500 g.[103] The authors noted that the overall ureaplasma colonization rate was 10% for full-term infants vs 24% for preterm infants. This variability likely reflects the causative role for these organisms in the onset of preterm labor.[104]

Ureaplasma spp. are a frequent cause of chorioamnionitis and fetal infection.[104] Acute infections in the neonatal period appear to be less frequent, although the lack of detection may be secondary to inadequate/inappropriate collection and processing of culture specimens. Nevertheless, neonatal pneumonia,[105] sepsis,[102] and meningitis,[106] secondary to *Ureaplasma* spp. have all been clearly described in the literature. Interestingly, colonization of preterm infants with *Ureaplasma* spp. has been linked to development of several significant morbidities, including bronchopulmonary dysplasia,[107] intraventricular hemorrhage,[108] and necrotizing enterocolitis.[109]

Conclusion

Our understanding of the breadth and diversity of bacterial species inhabiting the female genital tract has been primarily limited by the ability to detect them. Improvements in cultivation techniques and the development of molecular-based identification strategies have enabled us to recognize that the microbiota of the female genital tract is extraordinarily complex and dynamic in nature, with significant inter-individual variability. Interestingly, these methodologies have helped validate several important observations made in the late 1800s, including the protective role of vaginal lactobacilli and the importance of both endogenous and exogenous microbes in the pathogenesis of diseases. Continued exploration

of host and microbial factors will help clarify the pathophysiology of important perinatal conditions, including chorioamnionitis, and will likely lead to new strategies to prevent infection-related morbidity in women and newborns.

Acknowledgments

Funding sources None.

References

1. Williams, J. The bacteria of the vagina and their practical significance, based upon the bacteriological examination of the vaginal secretions of ninety-two pregnant women. Philadelphia: 1898.
2. Gönner. Über Mikroorganismen im Sekret der weiblichen Genitalien wahrend der Schwangerschaft und bei puerperalen Erkrankungen. Cent Gyn. 1887:444.
3. Döderlein A. Untersuchungen liber das Vorkomen von Spaltpilzen in den Lochien des Uterus und der Vagina gesunder und kranker Wiiehnerrinnen. Arch Gyn. xxxi(412)
4. Döderlein, A. Das Scheidensekret und seine Bedeutung für das Puerperalfieber. 1892.
5. Thomas S. Döderlein's bacillus: *Lactobacillus acidophilus*. J Infect Dis. 1928; 43:218–27.
6. Saigh JH, Sanders CC, Sanders WE Jr. Inhibition of *Neisseria gonorrhoeae* by aerobic and facultatively anaerobic components of the endocervical flora: evidence for a protective effect against infection. Infect Immun. 1978; 19:704–10. [PubMed: 415983]
7. Reid G, Bruce AW, McGroarty JA, Cheng KJ, Costerton JW. Is there a role for lactobacilli in prevention of urogenital and intestinal infections? Clin Microbiol Rev. 1990; 3:335–44. [PubMed: 2224835]
8. Linhares IM, Summers PR, Larsen B, Giraldo PC, Witkin SS. Contemporary perspectives on vaginal pH and lactobacilli. Am J Obstet Gynecol. 204:120, e1–5. [PubMed: 20832044]
9. Cruickshank R. Doderlein's vaginal bacillus: a contribution to the study of the lacto-bacilli. J Hyg (Lond). 1931; 31:375–81. [PubMed: 20475100]
10. Hunter CA Jr, Long KR, Schumacher RR. A study of Döderlein's vaginal bacillus. Ann NY Acad Sci. 1959; 83:217–26. [PubMed: 14405451]
11. Rogosa M, Sharpe ME. Species differentiation of human vaginal lactobacilli. J Gen Microbiol. 1960; 23:197–201. [PubMed: 14438406]
12. Pavlova SI, Kilic AO, Kilic SS, et al. Genetic diversity of vaginal lactobacilli from women in different countries based on 16S rRNA gene sequences. J Appl Microbiol. 2002; 92:451–9. [PubMed: 11872120]
13. Larsen B, Monif GR. Understanding the bacterial flora of the female genital tract. Clin Infect Dis. 2001; 32:e69–77. [PubMed: 11181139]
14. Clarridge JE 3rd. Impact of 16S rRNA gene sequence analysis for identification of bacteria on clinical microbiology and infectious diseases. Clin Microbiol Rev. 2004; 17:840–62. table of contents. [PubMed: 15489351]
15. Falsen E, Pascual C, Sjoden B, Ohlen M, Collins MD. Phenotypic and phylogenetic characterization of a novel *Lactobacillus* species from human sources: description of *Lactobacillus iners* sp. nov. Int J Syst Bacteriol. 1999; 49(Pt 1):217–21. [PubMed: 10028266]
16. Macklaim JM, Gloor GB, Anukam KC, Cribby S, Reid G. At the crossroads of vaginal health and disease, the genome sequence of *Lactobacillus iners* AB-1. Proc Natl Acad Sci USA. 108(Suppl 1):4688–95.
17. Vasquez A, Jakobsson T, Ahrne S, Forsum U, Molin G. *Vaginal lactobacillus* flora of healthy Swedish women. J Clin Microbiol. 2002; 40:2746–9. [PubMed: 12149323]
18. Burton JP, Cadieux PA, Reid G. Improved understanding of the bacterial vaginal microbiota of women before and after probiotic instillation. Appl Environ Microbiol. 2003; 69:97–101. [PubMed: 12513982]

19. Zhou X, Brown CJ, Abdo Z, et al. Differences in the composition of vaginal microbial communities found in healthy Caucasian and black women. ISME J. 2007; 1:121–33. [PubMed: 18043622]
20. Nam H, Whang K, Lee Y. Analysis of vaginal lactic acid producing bacteria in healthy women. J Microbiol. 2007; 45:515–20. [PubMed: 18176534]
21. Fredricks DN, Fiedler TL, Marrazzo JM. Molecular identification of bacteria associated with bacterial vaginosis. N Engl J Med. 2005; 353:1899–911. [PubMed: 16267321]
22. Hyman RW, Fukushima M, Diamond L, Kumm J, Giudice LC, Davis RW. Microbes on the human vaginal epithelium. Proc Natl Acad Sci USA. 2005; 102:7952–7. [PubMed: 15911771]
23. Ravel J, Gajer P, Abdo Z, et al. Vaginal microbiome of reproductive-age women. Proc Natl Acad Sci USA. 108(Suppl 1):4680–7.
24. Hummelen R, Fernandes AD, Macklaim JM, et al. Deep sequencing of the vaginal microbiota of women with HIV. PLoS One. 5(8):e12078. [PubMed: 20711427]
25. Srinivasan S, Liu C, Mitchell CM, et al. Temporal variability of human vaginal bacteria and relationship with bacterial vaginosis. PLoS One. 5(4):e10197. [PubMed: 20419168]
26. Wilson, M. Microbial inhabitants of humans: their ecology and role in health and disease. 1st edition. Cambridge University Press; Cambridge: 2004.
27. Teisala K. Endometrial microbial flora of hysterectomy specimens. Eur J Obstet Gynecol Reprod Biol. 1987; 26:151–5. [PubMed: 3666272]
28. Goplerud CP, Ohm MJ, Galask RP. Aerobic and anaerobic flora of the cervix during pregnancy and the puerperium. Am J Obstet Gynecol. 1976; 126:858–68. [PubMed: 793391]
29. Gardner GH. The more common pelvic inflections, their etiology, pathology, differential diagnosis, treatment and prevention. Northwest Med. 1935; 34:417.
30. Hemsell DL, Obregon VL, Heard MC, Nobles BJ. Endometrial bacteria in asymptomatic, nonpregnant women. J Reprod Med. 1989; 34:872–4. [PubMed: 2585386]
31. Cassell GH, Younger JB, Brown MB, et al. Microbiologic study of infertile women at the time of diagnostic laparoscopy. Association of *Ureaplasma urealyticum* with a defined subpopulation. N Engl J Med. 1983; 308:502–5. [PubMed: 6218407]
32. Stray-Pedersen B, Bruu AL, Molne K. Infertility and uterine colonization with *Ureaplasma urealyticum*. Acta Obstet Gynecol Scand. 1982; 61:21–4. [PubMed: 7046333]
33. Duff P, Gibbs RS, Blanco JD, St Clair PJ. Endometrial culture techniques in puerperal patients. Obstet Gynecol. 1983; 61:217–22. [PubMed: 6337355]
34. Moller BR, Kristiansen FV, Thorsen P, Frost L, Mogensen SC. Sterility of the uterine cavity. Acta Obstet Gynecol Scand. 1995; 74:216–9. [PubMed: 7900526]
35. Cowling P, McCoy DR, Marshall RJ, Padfield CJ, Reeves DS. Bacterial colonization of the non-pregnant uterus: a study of pre-menopausal abdominal hysterectomy specimens. Eur J Clin Microbiol Infect Dis. 1992; 11:204–5. [PubMed: 1396742]
36. Svenstrup HF, Fedder J, Abraham-Peskir J, Birkelund S, Christiansen G. *Mycoplasma genitalium* attaches to human spermatozoa. Hum Reprod. 2003; 18:2103–9. [PubMed: 14507829]
37. McDonald HM, Chambers HM. Intrauterine infection and spontaneous midgestation abortion: is the spectrum of microorganisms similar to that in preterm labor? Infect Dis Obstet Gynecol. 2000; 8:220–7. [PubMed: 11220481]
38. Dong Y, St Clair PJ, Ramzy I, Kagan-Hallet KS, Gibbs RS. A microbiologic and clinical study of placental inflammation at term. Obstet Gynecol. 1987; 70:175–82. [PubMed: 3601279]
39. Hillier SL, Witkin SS, Krohn MA, Watts DH, Kiviat NB, Eschenbach DA. The relationship of amniotic fluid cytokines and preterm delivery, amniotic fluid infection, histologic chorioamnionitis, and chorioamnion infection. Obstet Gynecol. 1993; 81:941–8. [PubMed: 8497360]
40. Naeye RL, Peters EC. Causes and consequences of premature rupture of fetal membranes. Lancet. 1980; 1(8161):192–4. [PubMed: 6101643]
41. Divers M. Prenatal microbiological risk factors associated with preterm birth. Br J Obstet Gynaecol. 1992; 99:781. [PubMed: 1294094]

42. Seong HS, Lee SE, Kang JH, Romero R, Yoon BH. The frequency of microbial invasion of the amniotic cavity and histologic chorioamnionitis in women at term with intact membranes in the presence or absence of labor. Am J Obstet Gynecol. 2008; 199:375, e1–5. [PubMed: 18928978]
43. Onderdonk AB, Hecht JL, McElrath TF, Delaney ML, Allred EN, Leviton A. Colonization of second-trimester placenta parenchyma. Am J Obstet Gynecol. 2008; 199:52, e1–10. [PubMed: 18313635]
44. Steel JH, Malatos S, Kennea N, et al. Bacteria and inflammatory cells in fetal membranes do not always cause preterm labor. Pediatr Res. 2005; 57:404–11. [PubMed: 15659699]
45. Hillier SL. Diagnostic microbiology of bacterial vaginosis. Am J Obstet Gynecol. 1993; 169(2 Pt 2):455–9. [PubMed: 8357044]
46. Eschenbach DA, Davick PR, Williams BL, et al. Prevalence of hydrogen peroxide-producing *Lactobacillus* species in normal women and women with bacterial vaginosis. J Clin Microbiol. 1989; 27:251–6. [PubMed: 2915019]
47. Klebanoff MA, Schwebke JR, Zhang J, Nansel TR, Yu KF, Andrews WW. Vulvovaginal symptoms in women with bacterial vaginosis. Obstet Gynecol. 2004; 104:267–72. [PubMed: 15291998]
48. Llahi-Camp JM, Rai R, Ison C, Regan L, Taylor-Robinson D. Association of bacterial vaginosis with a history of second trimester miscarriage. Hum Reprod. 1996; 11:1575–8. [PubMed: 8671507]
49. Eschenbach DA, Gravett MG, Chen KC, Hoyme UB, Holmes KK. Bacterial vaginosis during pregnancy. An association with prematurity and postpartum complications. Scand J Urol Nephrol Suppl. 1984; 86:213–22. [PubMed: 6336136]
50. Silver HM, Sperling RS, St Clair PJ, Gibbs RS. Evidence relating bacterial vaginosis to intraamniotic infection. Am J Obstet Gynecol. 1989; 161:808–12. [PubMed: 2782365]
51. Watts DH, Eschenbach DA, Kenny GE. Early postpartum endometritis: the role of bacteria, genital mycoplasmas, and *Chlamydia trachomatis*. Obstet Gynecol. 1989; 73:52–60. [PubMed: 2783262]
52. Taha TE, Hoover DR, Dallabetta GA, et al. Bacterial vaginosis and disturbances of vaginal flora: association with increased acquisition of HIV. AIDS. 1998; 12:1699–1706. [PubMed: 9764791]
53. Koumans EH, Kendrick JS. Preventing adverse sequelae of bacterial vaginosis: a public health program and research agenda. Sex Transm Dis. 2001; 28:292–7. [PubMed: 11354269]
54. Gardner HL, Dukes CD. New etiologic agent in nonspecific bacterial vaginitis. Science. 1954; 120(3125):853. [PubMed: 13216184]
55. Gardner HL, Dukes CD. *Haemophilus vaginalis* vaginitis: a newly defined specific infection previously classified non-specific vaginitis. Am J Obstet Gynecol. 1955; 69:962–76. [PubMed: 14361525]
56. Menard JP, Fenollar F, Henry M, Bretelle F, Raoult D. Molecular quantification of *Gardnerella vaginalis* and *Atopobium vaginae* loads to predict bacterial vaginosis. Clin Infect Dis. 2008; 47:33–43. [PubMed: 18513147]
57. Gelber SE, Aguilar JL, Lewis KL, Ratner AJ. Functional and phylogenetic characterization of Vaginolysin, the human-specific cytolysin from *Gardnerella vaginalis*. J Bacteriol. 2008; 190:3896–903. [PubMed: 18390664]
58. Swidsinski A, Mendling W, Loening-Baucke V, et al. An adherent *Gardnerella vaginalis* biofilm persists on the vaginal epithelium after standard therapy with oral metronidazole. Am J Obstet Gynecol. 2008; 198:97, e1–6. [PubMed: 18005928]
59. Patterson JL, Stull-Lane A, Girerd PH, Jefferson KK. Analysis of adherence, biofilm formation and cytotoxicity suggests a greater virulence potential of *Gardnerella vaginalis* relative to other bacterial-vaginosis-associated anaerobes. Microbiology. 2010; 156(Pt 2):392–9. [PubMed: 19910411]
60. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am J Med. 1983; 74:14–22. [PubMed: 6600371]
61. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. J Clin Microbiol. 1991; 29:297–301. [PubMed: 1706728]

62. Zhou X, Brotman RM, Gajer P, et al. Recent advances in understanding the microbiology of the female reproductive tract and the causes of premature birth. Infect Dis Obstet Gynecol. 2010 doi: 10.1155/2010/737425.
63. Hedges SR, Barrientes F, Desmond RA, Schwebke JR. Local and systemic cytokine levels in relation to changes in vaginal flora. J Infect Dis. 2006; 193:556–62. [PubMed: 16425135]
64. Fredricks DN, Fiedler TL, Thomas KK, Oakley BB, Marrazzo JM. Targeted PCR for detection of vaginal bacteria associated with bacterial vaginosis. J Clin Microbiol. 2007; 45:3270–6. [PubMed: 17687006]
65. Menard JP, Mazouni C, Fenollar F, Raoult D, Boubli L, Bretelle F. Diagnostic accuracy of quantitative real-time PCR assay versus clinical and Gram stain identification of bacterial vaginosis. Eur J Clin Microbiol Infect Dis. 29:1547–52. [PubMed: 20814710]
66. Spandorfer SD, Neuer A, Giraldo PC, Rosenwaks Z, Witkin SS. Relationship of abnormal vaginal flora, proinflammatory cytokines and idiopathic infertility in women undergoing IVF. J Reprod Med. 2001; 46:806–10. [PubMed: 11584481]
67. Krohn MA, Hillier SL, Nugent RP, et al. The genital flora of women with intraamniotic infection. Vaginal Infection and Prematurity Study Group. J Infect Dis. 1995; 171:1475–80. [PubMed: 7769281]
68. Donders G, Bellen G, Rezeberga D. Aerobic vaginitis in pregnancy. BJOG. June 14.2011 Epub ahead of print.
69. Donders GG, Vereecken A, Bosmans E, Dekeersmaecker A, Salembier G, Spitz B. Definition of a type of abnormal vaginal flora that is distinct from bacterial vaginosis: aerobic vaginitis. BJOG. 2002; 109:34–43. [PubMed: 11845812]
70. Donders GG, Van Calsteren K, Bellen G, et al. Predictive value for preterm birth of abnormal vaginal flora, bacterial vaginosis and aerobic vaginitis during the first trimester of pregnancy. BJOG. 2009; 116:1315–24. [PubMed: 19538417]
71. Rezeberga D, Lazdane G, Kroica J, Sokolova L, Donders GG. Placental histological inflammation and reproductive tract infections in a low risk pregnant population in Latvia. Acta Obstet Gynecol Scand. 2008; 87:360–5. [PubMed: 18307078]
72. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med. 2000; 342:1500–7. [PubMed: 10816189]
73. Gibbs RS, Duff P. Progress in pathogenesis and management of clinical intraamniotic infection. Am J Obstet Gynecol. 1991; 164(5 Pt 1):1317–26. [PubMed: 2035575]
74. Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clin Perinatol. 37:339–54. [PubMed: 20569811]
75. Hillier SL, Martius J, Krohn M, Kiviat N, Holmes KK, Eschenbach DA. A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. N Engl J Med. 1988; 319:972–8. [PubMed: 3262199]
76. Sperling RS, Newton E, Gibbs RS. Intraamniotic infection in low-birth-weight infants. J Infect Dis. 1988; 157:113–17. [PubMed: 3335795]
77. Djukic S, Nedeljkovic M, Pervulov M, Ljubic A, Radunovic N, Lazarevic B. Intra-amniotic *Chlamydia trachomatis* infection. Gynecol Obstet Invest. 1996; 42:109–12. [PubMed: 8878715]
78. DiGiulio DB, Romero R, Amogan HP, et al. Microbial prevalence, diversity and abundance in amniotic fluid during preterm labor: a molecular and culture-based investigation. PLoS One. 2008; 3:e3056. [PubMed: 18725970]
79. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci USA. 2010; 107:11971–5. [PubMed: 20566857]
80. Regan JA. Epidemiology of group B streptococcal colonization in pregnancy. Isr J Med Sci. 1983; 19:906–9. [PubMed: 6363347]
81. Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B streptococcal and *E. coli* disease continues. Pediatrics. 2011; 127:817–26. [PubMed: 21518717]
82. Dillon HC Jr, Gray E, Pass MA, Gray BM. Anorectal and vaginal carriage of group B streptococci during pregnancy. J Infect Dis. 1982; 145:794–9. [PubMed: 7045248]

83. Anthony BF, Okada DM, Hobel CJ. Epidemiology of group B streptococcus: longitudinal observations during pregnancy. J Infect Dis. 1978; 137:524–30. [PubMed: 351070]
84. Campbell JR, Hillier SL, Krohn MA, Ferrieri P, Zaleznik DF, Baker CJ. Group B streptococcal colonization and serotype-specific immunity in pregnant women at delivery. Obstet Gynecol. 2000; 96:498–503. [PubMed: 11004347]
85. Regan JA, Klebanoff MA, Nugent RP. The epidemiology of group B streptococcal colonization in pregnancy. Vaginal Infections and Prematurity Study Group. Obstet Gynecol. 1991; 77:604–10. [PubMed: 2002986]
86. Rocchetti TT, Marconi C, Rall VL, Borges VT, Corrente JE, da Silva MG. Group B streptococci colonization in pregnant women: risk factors and evaluation of the vaginal flora. Arch Gynecol Obstet. 283:717–21. [PubMed: 20349243]
87. Baker CJ. Group B streptococcal infections. Clin Perinatol. 1997; 24:59–70. [PubMed: 9099502]
88. Phares CR, Lynfield R, Farley MM, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999–2005. JAMA. 2008; 299:2056–65. [PubMed: 18460666]
89. Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B streptococcal and *E. coli* disease continues. Pediatrics. 2011; 127:817–26. [PubMed: 21518717]
90. Parm U, Metsvaht T, Sepp E, et al. Risk factors associated with gut and nasopharyngeal colonization by common Gram-negative species and yeasts in neonatal intensive care units patients. Early Hum Dev. 2011; 87:391–9. [PubMed: 21419584]
91. Glode MP, Sutton A, Robbins JB, et al. Neonatal meningitis due of *Escherichia coli* K1. J Infect Dis. 1977; 136(Suppl):S93–7. [PubMed: 330780]
92. Amstey MS, Lewin E, Colaice J. Vaginal colonization with invasive *Escherichia coli* during pregnancy. Am J Obstet Gynecol. 1980; 137:534–5. [PubMed: 6992581]
93. Sarff LD, McCracken GH, Schiffer MS, et al. Epidemiology of *Escherichia coli* K1 in healthy and diseased newborns. Lancet. 1975; 1(7916):1099–104. [PubMed: 49468]
94. Kinney JS, Johnson K, Papasian C, Hall RT, Kurth CG, Jackson MA. Early onset *Haemophilus influenzae* sepsis in the newborn infant. Pediatr Infect Dis J. 1993; 12:739–43. [PubMed: 8414801]
95. Tariq N, Jaffery T, Ayub R, Alam AY, Javid MH, Shafique S. Frequency and antimicrobial susceptibility of aerobic bacterial vaginal isolates. J Coll Physicians Surg Pak. 2006; 16:196–9. [PubMed: 16542599]
96. Martyn G. Staphylococci in the newborn; their coagulase production and resistance to penicillin and streptomycin. Br Med J. 1949; 1(4607):710–12. [PubMed: 18118583]
97. Bourgeois-Nicolaos N, Lucet JC, Daubie C, et al. Maternal vaginal colonisation by *Staphylococcus aureus* and newborn acquisition at delivery. Paediatr Perinat Epidemiol. 2010; 24:488–91. [PubMed: 20670229]
98. Andrews WW, Schelonka R, Waites K, Stamm A, Cliver SP, Moser S. Genital tract methicillin-resistant *Staphylococcus aureus*: risk of vertical transmission in pregnant women. Obstet Gynecol. 2008; 111:113–18. [PubMed: 18165399]
99. Top KA, Huard RC, Fox Z, et al. Trends in methicillin-resistant *Staphylococcus aureus* anovaginal colonization in pregnant women in 2005 versus 2009. J Clin Microbiol. 2010; 48:3675–80. [PubMed: 20686089]
100. Creech CB, Litzner B, Talbot TR, Schaffner W. Frequency of detection of methicillin-resistant *Staphylococcus aureus* from rectovaginal swabs in pregnant women. Am J Infect Control. 2010; 38:72–4. [PubMed: 19836855]
101. Waites KB, Katz B, Schelonka RL. Mycoplasmas and ureaplasmas as neonatal pathogens. Clin Microbiol Rev. 2005; 18:757–89. [PubMed: 16223956]
102. Waites KB, Crouse DT, Cassell GH. Systemic neonatal infection due to *Ureaplasma urealyticum*. Clin Infect Dis. 1993; 17(Suppl 1):S131–5. [PubMed: 8399903]
103. Kafetzis DA, Skevaki CL, Skouteri V, et al. Maternal genital colonization with *Ureaplasma urealyticum* promotes preterm delivery: association of the respiratory colonization of premature infants with chronic lung disease and increased mortality. Clin Infect Dis. 2004; 39:1113–22. [PubMed: 15486833]

104. Cassell GH, Waites KB, Watson HL, Crouse DT, Harasawa R. *Ureaplasma urealyticum* intrauterine infection: role in prematurity and disease in newborns. Clin Microbiol Rev. 1993; 6:69–87. [PubMed: 8457981]

105. Waites KB, Crouse DT, Philips JB 3rd, Canupp KC, Cassell GH. *Ureaplasma pneumonia* and sepsis associated with persistent pulmonary hypertension of the newborn. Pediatrics. 1989; 83:79–85. [PubMed: 2909979]

106. Garland SM, Murton LJ. Neonatal meningitis caused by *Ureaplasma urealyticum*. Pediatr Infect Dis J. 1987; 6:868–70. [PubMed: 3670956]

107. Wang EE, Ohlsson A, Kellner JD. Association of *Ureaplasma urealyticum* colonization with chronic lung disease of prematurity: results of a metaanalysis. J Pediatr. 1995; 127:640–4. [PubMed: 7562292]

108. Viscardi RM, Hashmi N, Gross GW, Sun CC, Rodriguez A, Fairchild KD. Incidence of invasive ureaplasma in VLBW infants: relationship to severe intraventricular hemorrhage. J Perinatol. 2008; 28:759–65. [PubMed: 18596706]

109. Okogbule-Wonodi AC, Gross GW, Sun CC, et al. Necrotizing enterocolitis is associated with ureaplasma colonization in preterm infants. Pediatr Res. 2011; 69(5 Pt 1):442–7. [PubMed: 21258263]

Practice points

- The microbiota of the female genital tract is extraordinarily complex and dynamic in nature, with significant inter-individual variability.
- Lactobacilli are the dominant organisms in the vaginal tract of most healthy premenopausal women.
- Disruption of the vaginal microbial community due to invasion of exogenous organisms or by overgrowth of one or more endogenous species is associated with adverse pregnancy outcomes.
- A number of potential neonatal pathogens may be found in the vaginal tissues of healthy women. Vertical transmission of these organisms is associated with increased risk for invasive bacterial disease in the newborn.

Research directions

- Exploration of bacteria–host interactions will help elucidate the underlying mechanisms leading to perinatal morbidities, including chorioamnionitis, and may lead to novel strategies to prevent infection-related morbidity in women and newborns.