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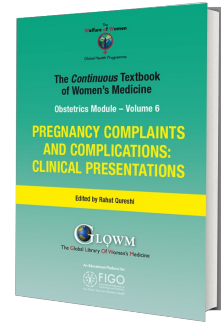
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PREGNANCY COMPLAINTS AND COMPLICATIONS: CLINICAL PRESENTATIONS

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Chapter

Vaginal Discharge

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INTRODUCTION

Presenting vaginal discharge or leucorrhea may correspond to a physiological event in women or be due to a pathological condition.¹ Differentiating the abnormal characteristics of vaginal discharge from its normal features may present a clinical challenge. Vaginal discharge varies in quantity, consistency and appearance between women and can be modified by various factors such as menstrual cycle phase, pregnancy and infection.²

Physiological changes in pregnancy increase in the amount of discharge, and generate a greater susceptibility to colonization and infection.³ The vast majority of pregnant women experience increased vaginal discharge and it is of significant clinical importance to identify and diagnose pathological conditions as these are associated with an increase in the risk of obstetric complications and must be treated promptly.¹

In recent years, there has been an increase in scientific interest in the vaginal microbiome. Owing to advances in molecular biology, its influence on the course of maternal and fetal health during pregnancy has been demonstrated, being involved in both physiological and pathological processes.⁴ Throughout this chapter we will discuss the normal vaginal microbiome and its changes during pregnancy, as well as the most frequent causes of pathological leucorrhea in pregnancy.

THE VAGINAL MICROBIOME

Vaginal microbiome is a dynamic microbial ecosystem that plays an important role in supporting a healthy vaginal environment.⁵ Under normal conditions, during the reproductive years, Gram-positive bacilli, *Lactobacillus* spp., dominate the vaginal flora.⁴ These microorganisms are known as fermenters as they take the degradation products of the glycogen deposited in the vaginal epithelium and use them through a fermentation process to produce lactic acid. The end result lowers vaginal pH and maintains it in a range from 3.5 to 4.5, thus creating an acidic and unfavorable environment for pathogenic microorganisms.⁵ This explains why the vaginal microbiome plays a key role in the defense against microbial urogenital infections such as bacterial vaginosis, yeast infections, sexually transmitted diseases, and pelvic inflammatory disease.⁴

The vaginal microbiome is influenced by numerous internal and external factors including age, menstrual cycle, contraception, antibiotics, and sexual activity. This causes the microbial composition of the female genital tract to vary dramatically over time and throughout a woman's life course in accordance to estrogen production.^{4,6} During perinatal development, maternal estrogens induce the growth and thickening of the vaginal epithelium as well as the deposit of glycogen in the epithelial cells. In the immediate extrauterine life, the absence of these estrogens results in a thinning of this mucosa, and therefore a reduction in fermenting microorganisms. At this time, the vaginal microbiota is dominated by Gram-negative anaerobic bacteria including: *Actinomyces*, *Bifidobacterium*, *Peptococcus*, *Peptostreptococcus*, and *Propionibacterium*, in addition to some aerobic bacteria such as: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus viridis*, and *Enterococcus viridis*. With the onset of puberty, estrogen gains control and the vaginal epithelium increases in thickness again and selects the growth of glucose-fermenting microorganisms. From this moment on, the vaginal microbiome becomes dominated by several species of lactobacilli. The microbiota of the adolescent girl, similarly to that of young woman, is dominated by *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus iners* and *Lactobacillus jensenii*. The composition of the postmenopausal vaginal microbiota is very similar to the premenopausal microbiota, with changes mainly in its diversity. During menopause, with the decrease of estrogen levels, the microbiota is dominated by *L. crispatus*, *L. iners*, *G. vaginalis*, and *Prevotella*, with a lower amount of *Candida* spp. and *Mobiluncus* spp., among others. However, longitudinal analyses show that the vaginal microbiota in post-menopause is stable and does not undergo significant changes in its diversity. Unlike the vaginal microbiota in premenopause, which constantly changes, shifting from one type of bacteria to another during menstrual cycle.⁴

THE VAGINAL MICROBIOME DURING PREGNANCY

Throughout pregnancy, women experience important hormonal, metabolic and immunological changes that are essential for normal fetal development.⁶ Among these changes, the lower genital tract experiences a thinning of the vaginal mucosa resulting in a greater surface area, making pregnant women more susceptible to vaginal infections.² It has been shown that during pregnancy, in addition to these physiological adaptations, significant changes arise in the microbiome of different organs, including the vaginal microbiome, on which we focus throughout this chapter.⁶

During pregnancy, the placenta produces high levels of estrogen that promote an increase in the secretion of glycogen to the vaginal epithelium. This favors the proliferation and dominance of *Lactobacillus* spp, thus promoting a healthy vaginal environment throughout pregnancy.⁷ The composition of the vaginal microbiome undergoes changes as pregnancy progresses. In general terms it is less variable and diverse than in non-pregnant women, and has a higher predominance of *Lactobacillus* spp.⁸ This stability hypothesis is explained by constant hormonal levels, the absence of menstrual bleeding and changes in sexual habits during pregnancy.⁷ The diversity of the vaginal microbiome is greater during the first trimester and decreases during the second and third trimesters, accordingly to the rise in estrogen levels as gestational age advances. Towards term, the microbiome changes once again and shifts towards a composition and diversity similar to that of the non-gestational state.^{7,9} Subsequently, the decrease in estrogen levels experienced in the postpartum period, results in a significant change characterized by a reduction in *Lactobacillus* spp.⁶

The clinical significance of these changes during pregnancy remains unclear and controversial. Studies have shown that gestational age, vaginal zone, and ethnicity influence the diversity of the vaginal microbiome during pregnancy, which in turn influences maternal-fetal health.⁶ Approximately 40–50% of preterm deliveries are associated with microbial etiologies.¹⁰ Recently, multiple studies have focused on the association of the vaginal microbiome during pregnancy and

the outcome of preterm delivery. Inflammation of the fetal membranes and placental chorion is typically generated by the ascent of bacteria from the lower genital tract towards the placenta, fetal membranes, and uterine cavity.^{6,10} This bacterial ascent has focused the attention of many studies onto the vaginal microbiome.^{7,8}

Genetic factors have been shown to determine the interaction between the microbiota and the host. The same microbial communities can generate different responses in women of different ethnic origins.⁷ Studies have revealed a spectrum of abnormalities in the vaginal microbiome which is associated with an increased risk of preterm delivery, yet this spectrum of alterations varies according to the population studied.¹⁰ A high diversity in the vaginal microbiome and a low lactobacilli count indicate vaginal dysbiosis in Caucasian women and has been associated with preterm birth.^{7,11} In contrast, African-American women, who have an overall higher risk of preterm delivery,¹² usually present a lower diversity in their vaginal microbiota during pregnancy.^{13,14} Despite controversies, in general terms, a dominance in the vaginal microbiome of *G. vaginalis*, *Ureaplasma* and *Prevotella* during pregnancy has been associated with obstetric complications, mainly preterm childbirth.^{8,15} Although it seems clear that the vaginal microbiome plays an important role and that changes in its composition are associated with preterm delivery, more studies are needed to establish the precise connection between the vaginal microbiome and preterm childbirth for specific populations.⁷

PREVALENT CAUSES OF PATHOLOGICAL LEUCORRHEA IN PREGNANCY

Due to the physiologic changes experienced during pregnancy, women present with an increase in their normal vaginal discharge, which is composed of water, electrolytes, epithelial cells, microorganisms, fatty acids and carbohydrate compounds. The clinical challenge is to differentiate this physiologic increase from a pathological leucorrhea that indicates alteration in the vaginal microbiome and infection.¹ Pathological vaginal discharge can cause adverse maternal-fetal outcomes² and hence the importance of an accurate diagnosis and timely treatment during pregnancy. We review the most prevalent causes of pathological leucorrhea in pregnancy, their diagnosis and treatment.

Bacterial vaginosis

Bacterial vaginosis (BV) is the most common vaginal dysbiosis in women of reproductive age.¹⁶ It represents the most common cause of vaginal discharge, accounting for almost half of all of the infectious vaginitis.¹⁷ In the United States, approximately one-third (29%) of women aged 14–49 have symptomatic or asymptomatic BV. Although its exact origin remains uncertain, it is known to be associated with alterations of the vaginal microbial environment.¹⁸ The prevalence of BV varies both internationally and within nations, with its prevalence ranging from 20 to 60% from country to country. In Africa the prevalence is high, with approximately 58%, while in regions such as Asia, Latin America, the Caribbean and the United States, its prevalence is moderate, reported in 23.2%. In Australia the prevalence is low, around 4.7%. It has been stipulated that cultural factors could play an important role in the development of this entity, but also differences in diagnostic techniques and clinical guidelines hinder the assessment of its true prevalence.¹⁶

Etiological agent

BV was initially called '*Haemophilus vaginalis* vaginitis' based on its believed etiological agent *H. vaginalis*, in 1955. Later, it was discovered that it did not belong to the genus *Haemophilus* and it was renamed *Gardnerella vaginalis*.¹⁹ As mentioned, its exact origin is still unknown, however, it is recognized that BV is polymicrobial disorder and a modification of the vaginal flora characterized by the overgrowth of opportunistic bacteria, such as Gram negative and facultative anaerobic bacilli: *Gardnerella vaginalis*, *Prevotella* spp., *Bacteroides* spp., *Mobiluncus* spp., Gram positive cocci, and genital *Mycoplasma* (*Mycoplasma hominis* and *Ureaplasma urealyticum*). This overgrowth is caused by a decrease in the levels of lactobacilli, which usually dominate a healthy vaginal microbiome, and the subsequent increase in vaginal pH.¹⁶ Therefore, BV represents a general change in the vaginal homeostasis, instead of a single definition for a specific change in the normal microbiome of the vagina.¹⁸

The vaginal microbiome and bacterial vaginosis

The vaginal microbiome has a direct correlation with BV. A normal microbiome has low pH and is dominated by *Lactobacillus* such as *L. crispatus*, *L. iners*, *L. gasseri* and *L. jensenii*. Studies have found that it is more common to find women with *L. iners* infected with BV compared to *L. crispatus*, which is more commonly found in women with healthy vaginal microbiome. Additionally, *Atopobium*, *G. vaginalis*, *Prevotella*, and *M. hominis* play an important role and were found to be the most prevalent bacteria among women with BV.²⁰ The metabolic profile of women with BV shows an increase in amines such as tyramine, trimethyltyramine and cadaverine, which are associated with a rise in the transudation and exfoliation of the vaginal squamous epithelial cells. This results in the formation of the diagnostic clue cells of BV.^{20,21} In addition, there have been four subgroups of *G. vaginalis* identified, which are being studied to be able to differentiate the pathogenic strains from the non-pathogenic ones, as well as their resistance to certain antibiotic treatments.²² This is why BV is not classified as a sexually transmitted infection, as there is no sole causative agent and a clear counterpart has not been established in men.²³

Risk factors

There are several risk factors associated with BV; these include multiple sexual partners, sex with women, and the presence of sexually transmitted infections, and certain races such as African and American women, in whom the prevalence is higher. Hormonal levels can also influence the presence of BV by altering the normal vaginal microbiome.²⁴ The incidence and prevalence of BV decreases significantly with the use of hormonal contraceptives, and recurrence was halved when using estrogen-containing contraceptive preparations. In addition, in postmenopausal women using hormone replacement therapy, *Lactobacillus* colonization increases and BV infection rates decrease.²⁵ Finally, tobacco use has also been linked with an increase in the vaginal bacteria associated with BV, this is thought to be due to the anti-estrogenic effect of smoking.²⁴

Diagnosis

In daily clinical practice, the Amsel criteria are used for the diagnosis of BV. For a positive diagnosis, three of the following four criteria must be present:

1. Homogeneous, fine, grayish-white discharge that gently covers the vaginal walls.
2. Vaginal pH >4.5
3. Positive amine odor test, defined as the presence of a fishy odor when a drop of 10% potassium hydroxide (KOH) is added to a vaginal discharge sample.
4. Presence of clue cells: scaly vaginal epithelial cells covered by adherent coccobacilli. For a positive result, at least 20% of the epithelial cells in the wet mount must be clue cells and these must be diagnosed by an experienced microbiologist, to be considered a reliable predictor of BV.¹⁸

Pregnancy-associated complications

Approximately one-third of pregnant women have either symptomatic or asymptomatic BV.¹⁸ Studies have shown that the presence of this condition during pregnancy is associated with important obstetrical complications. Different studies have shown an increase of at least twice the risk of preterm delivery potentially related to chorioamnionitis. Additionally, a 2.5 times increment in the risk of postpartum endometritis, and a 6.3 times the risk of miscarriage, have also been described.²⁶ However, routine screening for asymptomatic pregnant patients is not recommended by the different obstetric international societies.¹⁸

Vaginal pH as screening for vaginosis in pregnancy

Despite all efforts, preterm birth rates have not decreased satisfactorily over time. Due to the proven relationship of infectious agents with preterm delivery, multiple studies have been conducted in regards to screening and treatment during pregnancy. Various studies have described that the process cannot be reversed with antibiotics at a late stage, so efforts have centered on finding the best strategy for early detection and prompt treatment. In this attempt at early diagnosis, the measurement of vaginal pH for screening, then a subsequent medical diagnosis has been proposed. Hauth *et al.*, in a secondary analysis of asymptomatic patients with pregnancies of 8–22 weeks, found that patients with vaginal

pH ≥ 5 or ≥ 4.5 plus a Nugent score of 9–10, had a significant increase in the rates of preterm delivery (<37, <35 and <32 weeks) and birth weight less than 2500 g or less than 1500 g.²⁷

Hoyme, *et al.*, through a German provincial government initiative decided to promote the self-measurement of vaginal pH as a strategy to reduce the rates of preterm birth in the region. They reported a reduction in the rate of prematurity <32 weeks decreased from 1.46% to 1.31% and, finally, to 1.26% at the end of the study.²⁸ In addition, the rate of newborns <1500 g reduced from 1.48% to 1.22% and 1.15%, respectively. Provided that there is no safe, simple and inexpensive alternative method, measurement of intravaginal pH seems to be a simple option to detect women at risk and who need a specific diagnostic evaluation followed by efficient medical treatment. However promising, larger studies are needed to evaluate this screening method at a bigger-scale.²⁸

Routine screening and treatment for bacterial vaginosis in asymptomatic pregnant patients is not recommended

American College of Obstetricians and Gynecologists (ACOG). US Preventive Services Task Force (USPSTF). Centers for Disease Control and Prevention (CDC). Society of Obstetricians and Gynaecologists of Canada guidelines.

Treatment during pregnancy

Oral treatment is effective in reducing the signs and symptoms of vaginal infection and should be administered to all pregnant women with symptomatic BV. Treatment options include systemic formulations such as metronidazole 500 mg twice a day for 7 days, metronidazole 250 mg three times a day for 7 days, or clindamycin 300 mg, twice a day for 7 days.¹⁸ However, it is important to mention that treating the infection has not been proven to reduce the associated risk of preterm birth, regardless of the antibiotic regimen implemented.²⁹

Metronidazole is known to cross the placental barrier and therefore its use during pregnancy has been controversial; however, there are various studies that report its use as low risk during pregnancy. Multiple meta-analyses and systematic reviews published more than 25 years ago report its safety and absence of evidence of teratogenicity or mutagenic effects in children exposed *in utero*, even during the first trimester.^{30,31} The same has been proven true for systemic treatment with clindamycin.³² The use of Boric acid and tinidazole is not recommended during pregnancy because of their safety has not been determined.³³

Vulvovaginal candidiasis

Vulvovaginal candidiasis is the second most common cause of pathological vaginal discharge, and corresponds to 20–25% of all infectious vaginitis. Most women have at least one episode of candidal vulvovaginitis during their lifetime.³⁴ It is characterized by typical vaginal symptoms that include discharge and external vulvar inflammation.³⁵

Etiological agent and risk factors

The main etiological agent is *Candida albicans*, accounting for 90% of the infections. It is a diploid asexual fungus in the form of yeast, with an incubation period between 8 and 15 days.²⁹ *Candida* spp. and anaerobes are part of the normal microbiota in asymptomatic women and it is more common to have an infection with non-albicans strains of candida.³⁶ Among the risk factors that we can find in patients who develop this type of vaginitis are recent use of antibiotics, uncontrolled diabetes mellitus, HIV, use of corticosteroids and other immunosuppressions.³⁷ Pregnancy, for its part, due to the hormonal changes characterized by increased production of estrogens, increase in vaginal glycogen concentration, together with modulation of cellular immunity, is associated not only with higher rates of colonization, but also with higher rates of infection and recurrence.³⁸

Signs and symptoms

Typical symptoms consist of white, thick, lumpy vaginal discharge, associated with vulvar itching or burning, erythema and edema.³⁹

Diagnosis

Vulvovaginal candidiasis can be diagnosed by visualization of yeast hyphae in a potassium hydroxide preparation in women with symptoms. Women with yeast infections have an acidic vaginal pH, which is conducive to yeast's growth.⁴⁰

Pregnancy-associated complications

Although vulvovaginal candidiasis infection is common during pregnancy, it has not been clearly associated with premature delivery, low birth weight, or premature rupture of membranes (PROM).⁴¹ Intra-amniotic infection with candida has been reported, although with a very low frequency and usually associated with the presence of some intrauterine foreign body such as cerclage or IUD. Clinical manifestations of newborn infections range from small local compromise of the skin or mucosa, such as oropharyngeal infection (oral thrush), to severe systemic involvement. The latter, may present with necrosis of the brain, heart, lungs, kidneys and other. Congenital candidiasis typically manifests itself within the first 24 hours of life and is the product of an intrauterine infection or severe vaginal colonization at the time of labor and birth, with mechanisms similar to the agents involved in intraamniotic infection, which include the hematogenous route, invasion of membranes and ascending infection after rupture of membranes.⁴¹

Treatment

Treatment during pregnancy is aimed at reducing symptoms, for which the CDC recommends pregnant women be treated with topical azoles applied for 7 days.³⁸

Clotrimazole 1% cream intravaginally or miconazole 2% cream for 7 days are the most recommended regimens. These formulations have been studied and are deemed safe during pregnancy. Topical treatment is preferred over oral due to potential obstetrical risks with oral azoles such as miscarriage or fetal malformations, particularly at high doses.⁴²

Treatment of sexual partners is indicated in cases of recurrent vulvovaginitis or partners with clinical balanitis.²⁹

Trichomoniasis

Etiological agent and risk factors

Trichomoniasis is a sexually transmitted disease caused by *Trichomonas vaginalis*. This protozoan can remain latent for days or months and suddenly multiply, affecting the vagina, urethra and bladder. Its incubation period is 4–28 days.²⁹ Risk factors for developing trichomoniasis include low socioeconomic status, multiple sexual partners, other sexually transmitted diseases (STDs), unprotected sex, drug use, and smoking.³⁷

Signs and symptoms

Typical symptoms include a greenish or yellow vaginal discharge, usually described as foamy and malodorous, vaginal pain and discomfort. As for clinical signs, inflammation and a strawberry cervix may be reported.³⁹

Diagnosis

Trichomoniasis can be diagnosed by the identification of the mobile flagellum in microscopic evaluation of wet preparations. However, this needs to be analyzed quickly after taking the sample and has a very low sensitivity. CDC recommends considering a molecular nucleic acid amplification test (NAAT) for diagnosis of asymptomatic women at high risk for infection or symptomatic women. This test has a sensitivity of 95% and can be performed on endocervical, vaginal, or urine samples or on a liquid-based Pap smear.⁴⁰

Pregnancy-associated complications

Trichomoniasis has been associated with adverse pregnancy outcomes, including: low birth weight, preterm delivery and premature rupture of membranes. All symptomatic pregnant women, regardless of the trimester in pregnancy, should be diagnosed and treated.⁴³

Treatment

Treatment aims to lessen symptoms and reduce transmission. The recommended regimen consists of a single oral dose

of 2 g of metronidazole, at any stage during pregnancy. Once again, although metronidazole crosses the placenta, data suggest that it poses a low risk to pregnant women.⁴⁴

The treatment of sexual partners and ruling out of other STDs is also recommended; as is advising to abstain from sexual intercourse until the couple is treated and free of symptoms. An HIV-positive pregnant woman receiving treatment for trichomoniasis should be reassessed within 3 months after treatment.³⁶ Although perinatal transmission of trichomoniasis is rare, treatment can also prevent respiratory or genital infection of the newborn.²⁹

Mycoplasma–Ureaplasma Infections

The role of *Mycoplasma hominis* and *Ureaplasma urealyticum* in infections during pregnancy and their ability to infect the placenta and fetus has been controversial. In particular, the role in preterm birth has been associated with mechanisms related to the ability of these bacteria to produce inflammatory cytokines and trigger preterm labor of infectious origin.³⁸

Etiological agent

Experts in infectious diseases of the female genital tract have long studied the conjoined presence of *Mycoplasma hominis* and *Ureaplasma urealyticum*. It is known that they may be part of the normal flora of sexually active women, and prevalences of 80% for ureaplasmas and up to 20% for *Mycoplasma hominis* have been reported in normal asymptomatic women. Nevertheless, through molecular methods it has been proven that both may be linked to obstetric infections such as chorioamnionitis, salpingitis, bacterial vaginosis, and postpartum endometritis.^{45,46}

There is limited knowledge available on the precise pathogenic mechanisms used by these bacteria. *Mycoplasma hominis* and *Ureaplasma* spp. adhere weakly to cells through several adhesins. Moreover, when they infect the genital tract, urease produced by *Ureaplasma* spp. hydrolyzes into ammonia and *Mycoplasma hominis* breaks down arginine and produces ammonia. This results in a reduction of the acidity of vaginal pH and predisposes to mixed infection, especially with BV.⁴⁵

Pregnancy-associated complications

With regards to adverse maternal and neonatal outcomes during pregnancy, several studies have proven their association, particularly with preterm birth, low birth weight, amnionitis, amniotic fluid infection, and premature rupture of the membranes. When the diagnosis of chorioamnionitis has been reported histologically, *Ureaplasma urealyticum* is one of the microorganisms most commonly isolated from the amnion, placenta or amniotic fluid.⁴⁷

In a study of patients with premature rupture of membranes, *Ureaplasma urealyticum* was present in 96% of the cases, but was only found in 32% of women who did not experience rupture of the membrane. *Ureaplasma* bacterial invasion of amniotic fluid has also been associated with cervical insufficiency. In addition, when analyzing placentas from pregnancies complicated with spontaneous preterm birth before 32 weeks, 83% of the placentas with a positive culture for *Ureaplasma* showed histological chorioamnionitis, while only 30% of the placentas with a negative result for *Ureaplasma*, showed signs of chorioamnionitis.⁴⁶

Diagnosis

Development of molecular detection methods has been a great advantage for the diagnosis of these infections. Polymerase chain reaction (PCR) now allows the detection of these organisms with great specificity. The known obstetric consequences of infection have increased the determination of obstetricians to identify this type of infection. However, currently there is no general rule for screening for mycoplasmas in pregnancy. Some experts agree that, although there is no role for routine vaginal testing, their presence could be tested in combination with the screening for abnormal vaginal microflora. On the other hand, vulvovaginal testing for mycoplasma is considered useful in women with preterm labor or PPROM, and should ideally be combined with the detection of inflammatory markers in the amniotic fluid.^{45,46}

Treatment

The antibiotic treatment of choice is the macrolides erythromycin, azithromycin or clarithromycin; however, resistance to these has been demonstrated for some types of *Mycoplasma*. Macrolides are the only drugs that can be used safely during pregnancy to treat *Mycoplasma* or *Ureaplasma* infections. Their safety in pregnancy has been widely studied, and

they should be used with caution when clearly indicated. Azithromycin remains the drug of choice, but the better profile of josamycin and solithromycin may make these drugs preferred candidates in the future. More studies are needed to test for safe use during pregnancy.⁴⁵

Chlamydial infections

Chlamydial infection is one of the most common sexually transmitted diseases in the United States, with three million new infections annually and an incidence in pregnancy of 2–3%, being higher in certain most vulnerable groups.

Chlamydia infection can affect a number of organs, including the genitourinary tract.⁴⁸

Etiological agent

The chlamydia group corresponds to small Gram-negative cocci that infect the squamous cell epithelium, in which *Chlamydia trachomatis* is the main species. *C. trachomatis* is known to have more than 18 serotypes, serotypes D to K are the ones associated with genital tract infections. Transmission is through direct contact, where an infected male patient can transmit the infection to 25% of his sexual partners, as well as vertical transmission in 50–60% of cases, especially in the second phase of labor.³⁸

Signs and symptoms

Unlike other sexually transmitted diseases, *C. trachomatis* can be asymptomatic in most of the population (80%). Symptoms can include vaginal discharge, vaginal bleeding after sexual activity or not related to menstruation, dyspareunia, among others.³⁸

Diagnosis

Culture of *C. trachomatis* obtained by endocervical and vaginal swabs is the only recommended medium for the diagnosis by direct immunofluorescence (DFI), enzyme immunoassay (EIA) and nucleic acid amplification techniques. Nucleic acid amplification techniques (NAATs) have very good sensitivity and specificity for the study of *C. trachomatis*, being able to identify patients with low inocula of the microorganism and in urinary samples where an invasive test is not required. Within this group is the PCR technique, TMA (transcription-mediated amplification).³⁸

Pregnancy-associated complications

There is no clear proven association of infection with *C. trachomatis* during pregnancy and obstetric complications such as preterm birth or PPRM, as studies have reported contradictory results.⁴⁹ In the newborn, the infection can cause neonatal conjunctivitis and pneumonia, and should always be considered when treating newborns with atypical pneumonia.³⁸

Screening during pregnancy

Since chlamydial infections are frequently asymptomatic, screening programs are believed essential to control infection and to prevent adverse sequelae, especially during pregnancy. However, policies and guidelines regarding screening vary among different countries. The US CDC recommends screening pregnant patients under the age of 25 or over 25 with risk factors for chlamydial infection. Canada recommends screening all pregnant patients, while the UK does not recommend routine screening during pregnancy. Also, there is controversy as to whether screening in the first or third trimester is appropriate, since in the first trimester it can prevent adverse effects in pregnancy and during the last one can prevent postnatal complications, for which more studies are warranted. More studies are needed to clarify further the requirement of screening and treatment of chlamydia during pregnancy.^{29,50}

Treatment

The CDC's recommended regimens for *C. trachomatis* infection during pregnancy is Azithromycin 1 mg PO in a single dose, reporting clinical experience and published studies for its safety and efficacy during pregnancy. Alternative regimens include amoxicillin 500 mg PO 3/day × 7 days, erythromycin 500 mg PO 4/day × 7 days and erythromycin ethylsuccinate (syrup) 800 mg – PO 4/day × 7 days.

CONCLUSION

The vaginal microbiome during pregnancy plays an important role in maternal-fetal health, as different alterations are associated with adverse obstetrical outcomes. In recent years, studies have shown the great influence that the vaginal microbiome has in neonatal health, due to the increased incidence of preterm delivery and intra-amniotic infection in the presence of alterations. It has now been recognized that the most prevalent conditions do not arise from infections of external origin, but on the contrary, arise from alterations in the vaginal microbiome during pregnancy. This is why the increase of vaginal discharge during pregnancy must be truly understood, and the identification and treatment of pathological causes must be pursued, as there is a necessity to regain balance in the vaginal microbiome during pregnancy.

PRACTICE RECOMMENDATIONS

- **The majority of pregnant women present with an increase in vaginal discharge. It is important to be able to differentiate the physiological discharge from a pathological underlying cause.**
- **Routine screening for bacterial vaginosis is not recommended in asymptomatic patients.**
- **Bacterial vaginosis should be treated in all symptomatic pregnant women with systemic formulations such as metronidazole 500 mg twice a day for 7 days, or clindamycin 300 mg, twice a day for 7 day.**
- **Topical azoles for 7 days (clotrimazole 1% cream intravaginally or miconazole 2% cream) are the most recommended regimens for treating vulvovaginal candidiasis during pregnancy.**
- **The recommended regimen for trichomoniasis consists of a single oral dose of 2 g of metronidazole, at any stage during pregnancy.**
- **Infection with *Chlamydia trachomatis* should be treated with azithromycin 1 g orally in a single dose.**

CONFLICTS OF INTEREST

The authors of this chapter declare that they have no interests that conflict with the contents of the chapter.

REFERENCES

- 1 Ibrahim SM, Bukar M, Audu BM. Management of Abnormal Vaginal Discharge in Pregnancy. In: *Genital Infections and Infertility* 2016.
- 2 Almubarak S, Alsoufyani A, Ahmed A, et al. Increased vaginal discharge during pregnancy: prevalence, causes, and associated symptoms. *Int J Med Dev Ctries* 2020.
- 3 Tatti S. Capítulo 4. Ecosistema vaginal normal. In: *Enfermedades de la vulva, la vagina y la región anal. Editorial Medica Panamericana* 2013.
- 4 Younes JA, Lievens E, Hummelen R, et al. Women and Their Microbes: The Unexpected Friendship. *Trends in Microbiology* 2018.
- 5 Greenbaum S, Greenbaum G, Moran-Gilad J, et al. Ecological dynamics of the vaginal microbiome in relation to health and disease. *American Journal of Obstetrics and Gynecology* 2019.
- 6 Taddei CR, Cortez RV, Mattar R, et al. Microbiome in normal and pathological pregnancies: A literature overview. In: *American Journal of Reproductive Immunology* 2018.
- 7 Kervinen K, Kalliala I, Glazer-Livson S, et al. Vaginal microbiota in pregnancy: Role in induction of labor and seeding the neonate's microbiota? *Journal of biosciences* 2019.
- 8 DiGiulio DB, Callahan BJ, McMurdie PJ, et al. Temporal and spatial variation of the human microbiota during pregnancy. *Proc Natl Acad Sci USA* 2015.
- 9 Rasmussen MA, Thorsen J, Dominguez-Bello MG, et al. Ecological succession in the vaginal microbiota during pregnancy and birth. *ISME J* 2020.
- 10 Fettweis JM, Serrano MG, Brooks JP, et al. The vaginal microbiome and preterm birth. *Nat Med* 2019.
- 11 Freitas AC, Chaban B, Bocking A, et al. The vaginal microbiome of pregnant women is less rich and diverse, with lower prevalence of Mollicutes, compared to non-pregnant women. *Sci Rep* 2017.
- 12 Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. *The Lancet* 2008.
- 13 Hyman RW, Fukushima M, Jiang H, et al. Diversity of the vaginal microbiome correlates with preterm birth. *Reprod Sci* 2014.
- 14 Tabatabaei N, Eren AM, Barreiro LB, et al. Vaginal microbiome in early pregnancy and subsequent risk of spontaneous preterm birth: a case-control study. *BJOG An Int J Obstet Gynaecol* 2019.
- 15 Critchley HOD, Babayev E, Bulun SE, et al. "Menstruation: Science and Society." *Am J Obstet Gynecol [Internet]* 2020. Available from: <http://www.sciencedirect.com/science/article/pii/S0002937820306190>
- 16 Coudray MS, Madhivanan P. Bacterial vaginosis – A brief synopsis of the literature. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2020.
- 17 Morris M, Nicoll A, Simms I, et al. Bacterial vaginosis: A public health review. *British Journal of Obstetrics and Gynaecology* 2001.
- 18 Reiter S, Kellogg Spadt S. Bacterial vaginosis: a primer for clinicians. *Postgraduate Medicine* 2019.
- 19 Hay P. Bacterial vaginosis. *Medicine (United Kingdom)*, 2014.
- 20 Vitali B, Cruciani F, Picone G, et al. Vaginal microbiome and metabolome highlight specific signatures of bacterial vaginosis. *Eur J Clin Microbiol Infect Dis* 2015.
- 21 Hodiwala A. Bacterial Vaginosis. *Int J Curr Microbiol Appl Sci* 2015;4(6):530–8.
- 22 Janulaitiene M, Paliulyte V, Grinceviciene S, et al. Prevalence and distribution of Gardnerella vaginalis subgroups in women with and without bacterial vaginosis. *BMC Infect Dis* 2017.
- 23 Bradshaw CS, Walker SM, Vodstrcil LA, et al. The influence of behaviors and relationships on the vaginal microbiota of women and their female partners: The WOW health study. *J Infect Dis* 2014.
- 24 Wilson JD, Lee RA, Balen AH, et al. Bacterial vaginal flora in relation to changing oestrogen levels. *Int J STD AIDS* 2007.
- 25 Muhleisen AL, Herbst-Kralovetz MM. Menopause and the vaginal microbiome. *Maturitas* 2016.
- 26 Leitich H, Kiss H. Asymptomatic bacterial vaginosis and intermediate flora as risk factors for adverse pregnancy outcome. *Best Practice and Research: Clinical Obstetrics and Gynaecology* 2007.
- 27 Hauth JC, MacPherson C, Carey JC, et al. Early pregnancy threshold vaginal pH and Gram stain scores predictive of subsequent preterm birth in asymptomatic women. *Am J Obstet Gynecol* 2003.
- 28 Hoyme UB, Hesse M. Reduced incidence of early preterm birth in the State of Thuringia following an intravaginal pH-self-monitoring screening program. *Arch Gynecol Obstet [Internet]* 2020;1–4. Available from: <https://doi.org/10.1007/s0040404&020-05574-7>
- 29 Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines. *MMWR Recomm Reports* 2015.
- 30 Burtin P, Taddio A, Ariburnu O, et al. Safety of metronidazole in pregnancy: A meta-analysis. *Am J Obstet Gynecol* 1995;172(2 PART 1):525–9.
- 31 Caro-Patón T, Carvajal A, De Diego IM, et al. Is metronidazole teratogenic? A meta-analysis. *Br J Clin Pharmacol* 1997;44(2):179–82.
- 32 Lamont RF, Nhan-Chang CL, Sobel JD, et al. Treatment of abnormal vaginal flora in early pregnancy with clindamycin for the prevention of spontaneous preterm birth: A systematic review and metaanalysis. *American Journal of Obstetrics and Gynecology* 2011.
- 33 Jayaram PM, Mohan MK, Konje J. Bacterial vaginosis in pregnancy – a storm in the cup of tea. *Eur J Obstet Gynecol Reprod Biol* 2020;253:220–4.
- 34 Sobel JD. Vaginitis. *New England Journal of Medicine* 1997.
- 35 ACOG Committee on Practice Bulletins–Gynecology. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists, Number 72, May 2006: Vaginitis. *Obstet Gynecol* 2006.
- 36 Paladine HL, Desai UA. Vaginitis: Diagnosis and Treatment. *Am Fam Physician* 2018;97(5):321–9.
- 37 Hainer BL, Gibson MV. Vaginitis. *Am Fam Physician* 2011;83(7):807–15.
- 38 Pradenas AM. Infecciones cervico vaginales y embarazo. *Rev Medica Clínica Clínica Condes* 2014;25(6):925–35.
- 39 Farage MA, Miller KW, Ledger WJ. Determining the cause of vulvovaginal symptoms. *Obstetrical and Gynecological Survey* 2008.
- 40 Chatwani AJ, Mehta R, Hassan S, et al. Rapid testing for vaginal yeast detection: a prospective study. *Am J Obstet Gynecol* 2007.
- 41 Roqué H, Abdelhak Y, Young BK. Intra amniotic candidiasis. Case report and meta-analysis of 54 cases. *In Journal of Perinatal Medicine* 1999.
- 42 Mølgaard-Nielsen D, Svanström H, Melbye M, et al. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA – J Am Med Assoc* 2016.

- 43 Cotch MF, Pastorek JG, Nugent RP, *et al.* Trichomonas vaginalis associated with low birth weight and preterm delivery. *Sex Transm Dis* 1997.
- 44 Briggs GG, Freeman RK. Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk: 10th edn *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk: Tenth Edition* 2014.
- 45 Donders GGG, Ruban K, Bellen G, *et al.* Mycoplasma/Ureaplasma infection in pregnancy: To screen or not to screen *Journal of Perinatal Medicine* 2017.
- 46 Larsen B, Hwang J. Mycoplasma, Ureaplasma, and adverse pregnancy outcomes: A fresh look. *Infectious Diseases in Obstetrics and Gynecology* 2010.
- 47 Hillier SL, Martius J, Krohn M, *et al.* A Case-Control Study of Chorioamnionic Infection and Histologic Chorioamnionitis in Prematurity *N Engl J Med* 1988.
- 48 Chlamydia screening among sexually active young female enrollees of health plans-United States, 2000-2007. *MMWR Morb Mortal Wkly Rep* 2009;58(14):362-5.
- 49 Adamson PC, Klausner JD. Treating chlamydial infections in pregnancy and preventing adverse birth outcomes *Lancet Infect Dis [Internet]* 2020;18(4):368-9. Available from: [http://dx.doi.org/10.1016/S1473-3099\(18\)30049-5](http://dx.doi.org/10.1016/S1473-3099(18)30049-5)
- 50 Chen X. Adverse pregnancy outcomes due to Chlamydia trachomatis Constantly high incidence of scarlet fever in Germany *Lancet Infect Dis [Internet]* 2020;18(5):499. Available from: [http://dx.doi.org/10.1016/S1473-3099\(18\)30211-1](http://dx.doi.org/10.1016/S1473-3099(18)30211-1)