

# Genital infections during pregnancy

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## Abstract

Genital infections during pregnancy are a major health problem in many parts of the world, with the particularity of being responsible for complications to the mother and infant, on top of being a burden to the health system. This chapter will be a discussion of the main genital infections during pregnancy: candidiasis, trichomoniasis, herpes, chlamydia, gonorrhea, bacterial vaginosis, aerobic vaginitis and human papillomavirus. Many of their complications are pregnancy-related for which a prompt diagnosis, effective treatment, and decrease in the risk of re-infection are critical in order to decrease their potential morbid-mortality. Management of these pathologies depends on the etiology, stage of infection, gestation, and any drug contraindication. After a systematic literature search followed by selection of the most relevant articles, recommendations for diagnosis and treatment of genital infections in pregnancy were developed.

## Summary of recommendations

1. Vulvovaginal candidiasis
  1. Candida colonization should be considered a risk factor for preterm birth as patients with untreated, asymptomatic vulvovaginal candidiasis have a higher spontaneous preterm birth rate when compared to those without candidiasis (GoR B).
  2. While topic or oral azoles are prescribed in non-pregnant women with good therapeutic cure rates, oral azoles are contraindicated during pregnancy (GoR B).
  3. A 6-day course of topic clotrimazole is recommended for candida eradication in pregnancy (GoR A).
2. Trichomoniasis
  1. Clinical findings along with identification of the parasite in wet-mount smear are sufficient to confirm the diagnosis (GoR A).
  2. No evidence supports the use of metronidazole in pregnant asymptomatic women as there seems to be no reduction in preterm birth or improve low birth weight even as it clears the infection (GoR A).
  3. Although one trial showed an increased tendency towards preterm birth and low birth weight on patients treated with metronidazole, there's a clear association with preterm delivery and preterm rupture of membranes in pregnant symptomatic women that aren't treated. The findings from the aforementioned trial are difficult to explain and co-infections might have been missed, thus, treatment is suggested (GoR A).
  4. The treatment of choice for Trichomonas is metronidazole 500 mg taken orally twice a day for 5 to 7 days. Alternate regimens are metronidazole 2 g in a single dose taken orally or as vaginal ovules at night for 5 days (GoR A).
  5. Metronidazole given as a single dose is likely to provide parasitological cure for Trichomoniasis, but the effect on pregnancy outcome is still unknown. (GoR A)
  6. Sexual partners should be treated simultaneously and sex should be avoided for a week after treatment has been completed. Further testing is recommended if symptoms remain (GoR C).
3. Herpes
  1. Since clinical diagnosis isn't sensitive or specific, pregnant women who present with symptoms should undergo serologic testing (both IgG and IgM) and viral identification by culture, PCR, or direct antibody fluorescence to identify the category and subtype of HSV infection (GoR C).
  2. Routine screening of asymptomatic women for HSV during pregnancy isn't recommended (GoR A).
  3. Cesarean section performed before rupture of membranes is advised after 34 weeks in all

- suspected cases of infection or in recurrent cases with lesions or prodromic symptoms (GoR B).
4. Prophylactic acyclovir is advised from 36 weeks onwards at a dosage of 400 mg three times a day, and continued after delivery (GoR B).
  5. Vaginal delivery is recommended in recurrent cases since there's a low estimated transmission rate (GoR B).
4. Chlamydia
1. Screening for Chlamydia and treating high-risk pregnant women can reduce the rate of adverse outcomes during pregnancy, such as ectopic pregnancies and PID (GoR B).
  2. Current suggested treatments during pregnancy are: Azithromycin 1 g orally single dose; Erythromycin 500 mg orally 4 times a day for 7 days, or Amoxicillin 500 mg orally 3 times a day for 7 days (GoR A).
  3. Oral azythromycin is the most effective, followed by erythromycin and finally amoxicillin. The single-dosage of azythromycin is thought to be responsible for this difference (GoR A).
  4. It is suggested to avoid sexual intercourse with current partners until a week after the patient and partner have finished treatment. Post-treatment testing is suggested in pregnant patients due to reduced efficacy of treatment and possibility of re-infection (GoR C).
5. Gonorrhea
1. A single dose of 250 mg of ceftriaxone is recommended in pregnancy (GoR A).
  2. A treatment regimen of 1 g azithromycin combined with 400 mg of cefixime has also been suggested in order to treat both Gonorrhea and Chlamydia given the high risk of possible co-infection (GoR A).
  3. Post-treatment testing can be performed after 4 weeks, with extended partner treatment and re-treatment when necessary (GoR C).
6. Bacterial vaginosis
1. Although vaginal pH testing is a quick and inexpensive test, there are other diagnostic methods. Diagnosis can be made using Amsel criteria and by laboratory testing (GoR A).
  2. Screening and treatment should be started since the first trimester, given that BV is associated to an increased risk of spontaneous abortion and early pregnancy loss (GoR B).
  3. Metronidazole can be used as a 2 g single dose, as 500 mg twice a day for 5 days or as 250 mg three times a day for 5 to 7 days. Although the latter is the recommended regime by the CDC, evidence is against low dose regimens during pregnancy (GoR A).
  4. Oral treatment is preferred since the prevention of preterm birth is better with this type of treatment (GoR A).
  5. Post-treatment testing is required due to a high rate of recurrence and despite a good pharmacological eradication rate (GoR B).
7. Aerobic vaginitis
1. (No recommendations due to lack of clinical studies)
8. Chorioamnionitis
1. GBS standardized screening should be performed in order to continue the decrease in morbimortality of this etiology in pregnant women (GOR A).
  2. Antibiotic treatment should be reserved to patients with diagnosis of clinical chorioamnionitis (GoR A).
  3. IV antibiotics are the treatment of choice, with PO antibiotics reserved only if the former aren't available (GoR A).
  4. In the setting of PPRM, treatment should be limited to 2 days of IV antibiotics followed by 5 days of PO antibiotics. Use beyond this period has no clinical benefit and presents worse neonatal outcomes (GoR A).
9. Group A streptococcus
1. Screening of pregnant women for GAS before delivery isn't recommended (GoR C).
  2. Use of the laboratory risk indicator for necrotizing fasciitis can help recognize NF in its early stages, but it doesn't delay surgical removal of the infected tissue (GoR C).
  3. Penicillin is the first line of treatment when administered early or after a low organism inoculum; clindamycin should be considered if administered late or after a high organism inoculum. In the setting of severe GAS infections, NF and STSS, penicillin and clindamycin should be given in combination (GoR B).
  4. Both IVIG and hyperbaric oxygen therapy have been suggested as adjunctive therapy,

however a cost:benefit ratio should be considered in each individual case (GoR C).

#### 10. HPV

1. Cesarean section is associated with a significantly lower relative risk of transmission when compared to vaginal delivery (GoR A).
2. High-risk HPV testing can be considered as a screening tool in low-income populations because its sensitivity and reliability to detect pre-cancer and early cancer are greater than that of cytology, potentially helping reduce cervical cancer rates [1] (GoR B).
3. Both urine and vaginal swab samples can be used for high-risk HPV testing. Self-samples or urine based testing have shown a greater acceptability among patients, while maintaining good diagnostic performance (GoR B).

## 1 Introduction

Genital infections during pregnancy are a major health problem in many parts of the world, with the particularity of being responsible for complications to the mother and infant, on top of being a burden in the health system. In addition, co-infection by more than one pathogen in pregnancy can increase the infectiousness and susceptibility of the etiological agent significantly. Many of the complications they bring are pregnancy-related, for which a prompt diagnosis, effective treatment, and reduction of the risk of re-infection are critical in order to decrease their potential morbi-mortality.

Infection during pregnancy can go unnoticed and has catastrophic consequences in the mother and fetus, with some of the most common complications being: ascending infection, chorioamnionitis, premature rupture of membranes, preterm delivery, low birth weight, and maternal sepsis. Vertical transmission can be transplacental, intrapartum, or postpartum.

Some risk factors for STDs include age under 25, high number of sexual partners, new sexual partners during pregnancy, living in high prevalence areas, intravenous drug use, and commercial sex. A thorough sexual history should be made in the first prenatal visit in order to establish a woman's risk and identify any high risk partners, such as those with known or suspected STDs or men who have sex with men [2].

Management of these pathologies depends on the etiology, stage of infection, gestational age, and any treatment contraindication. Both abstinence while the treatment is being received, treatment of the partner and test of cure is advised in most cases, in order to increase its effectiveness and avoid most complications at an early stage.

A barrier that can often be seen is the reluctance of a pregnant patient to undergo treatment for these diseases due to a perception that most drugs increase the risk of deleterious effects on fetal health, while in reality it is the opposite. In addition, some drugs can have a reduced tolerability, sometimes due to the need of a higher dosage during pregnancy. Both factors contribute to an increase in the rate of sub-treatment, putting at risk the well being of the newborn or the mother.

In the following pages the most common and important genital infections during pregnancy will be discussed, as well as their epidemiology, etiology, implications in pregnancy, treatment, and a view to the future.

## 2 Methods

A systematic literature search was performed for the last 20 years in Pubmed and Cochrane with the following key words: genital infections AND pregnancy; STI AND pregnancy; STD AND pregnancy; Candidiasis AND pregnancy; *Candida albicans*/C. albicans AND pregnancy; *Candida glabrata*/C. glabrata AND pregnancy; *Trichomonas* AND pregnancy; Herpes AND pregnancy; HSV AND pregnancy; *Neisseria gonorrhoeae*/N. gonorrhoeae AND pregnancy; HPV AND pregnancy; Bacterial Vaginosis/BV AND pregnancy; Aerobic Vaginitis/AV AND pregnancy. The following were the imitations: Publications should at least have the abstract available in English, and publications relevant to the fields of Gynecology and Obstetrics, Neonatology and Infectology were included.

All the potentially useful publications were screened by title, authors and abstract. After exclusion of duplicates and dismissal of those that weren't relevant, a total of 57 were included into the review, supplemented by citations or known to the authors.

The studies were rated according to the level of evidence and the strength of recommendations graded according to a system used in the EAU guidelines (2015) modified from the Oxford Centre for Evidence-

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based Medicine [2].

## 3 Results

### 3.1 Vulvovaginal candidiasis

Around 75% of all women will present at least one episode of vulvovaginal candidiasis during their lifetime, with *Candida albicans* being the most common species implicated, in around 85% of the cases, followed by *Candida glabrata*. Vulvovaginal candidiasis usually presents with a classic white, curdy, copious vaginal discharge. Infection during pregnancy is estimated as twice of that of non-pregnant women (LoE 3) [3], [4], [5]. This is thought to be due to physiologic changes, such as elevated hormone levels, decreased cellular immunity, reduced vaginal pH and increased vaginal glycogen concentration, all of which improve the environment for *Candida* colonization and overgrowth. Vulvovaginal candidiasis in pregnancy has also been associated to several complications during pregnancy and an adverse pregnancy outcome [3], [4], [5], [6].

A positive association between *Candida* colonization and *T. vaginalis* infection has been reported in a large multicenter cohort of over 13,000 pregnant women, while not being associated with demographic and behavioral risk factors indicative of sexually transmitted infections [5] (LoE 1b).

Carriage rates in pregnant women range from 18–38%, with amniotic fluid invasion in the presence of intact membranes ranging from 0.8–2% [5] (LoE 1b). Previously it was believed that asymptomatic colonization didn't warrant treatment, given that microbiological eradication is infrequent and that there were no significant sequelae associated with this state neither in pregnant nor in non-pregnant women [7]. However, it has been proven that patients with untreated, asymptomatic VVC have a higher spontaneous preterm birth rate when compared to those without candidiasis, which is consistent with *Candida* colonization as a risk factor for preterm birth (LoE 3; GoR B) [4].

Regarding treatment, while topical or oral azoles are prescribed in non-pregnant women with good therapeutic cure rates, oral azoles are contraindicated during pregnancy [7] (LoE 3; GoR B). Clotrimazole is classified as a category A drug, with only some skin reactions (burning, stinging or redness) that can occur occasionally. In addition, patients treated with clotrimazole had a tendency towards a reduction in preterm birth [4]. Topical azoles are more effective than nystatin and achieve acceptable cure rates, even when a 7-day course might be necessary [6]. Even though therapeutic response is reduced when compared with women who aren't pregnant, a 6-day course has been supported by the Cochrane Systemic Review for *Candida* eradication in pregnancy (LoE 1a; GoR A) [6], [8], [9]. If the clinical picture is that of an invasive candidiasis, systemic amphotericine B is the treatment of choice [10].

### 3.2 Trichomoniasis

*Trichomonas vaginalis* is recognized as one of the most common non-viral sexually transmitted infections. Its prevalence in the USA is estimated at 2.3 million (3.1%) in the group of women from 14–49, with nearly 85% being asymptomatic, while in Africa and the Americas prevalence is up to 20% (LoE 3). However, when looking at world data, around 153 million cases with *Trichomonas vaginalis* were present at any point in 2005 [11]. The organism can be found in the vagina, urethra and paraurethral glands, with the infection being characterized by pruritus, dysuria, dyspareunia, purulent green or frothy yellow discharge, as well as vulvo-vaginitis and a “strawberry” cervix on speculum examination, although infection can also cause pelvic pain or vulvar ulceration [2], [12]. Although some evidence points at association with preterm delivery, low birth weight and maternal postpartum sepsis, further research is needed before confirming that association. As well, there's no evidence that suggests puerperal infection or neonatal effects (LoE 3) [2].

Women with no history of sexual intercourse can also present trichomoniasis (1.0%), as well as women who have never been pregnant (4.1%) and finally pregnant women (3.2%) [12] (LoE 3). There are sensitive diagnostic tools available, such as immunofluorescence, enzyme immunoassay or culture, although they are more time consuming, costly and rarely used. Clinical findings along with identification of the parasite in wet-mount smear are sufficient to confirm the diagnosis [12] (LoE 1a; GoR A).

Although spontaneous cure rate reaches 20–25% (LoE 3), both developing and developed countries have to deal with the burden of Trichomoniasis during pregnancy, as well as with its effects on pregnancy and the safety and effectiveness of multiple treatment protocols. Metronidazole is regarded as an

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effective treatment for clearing the infection by *Trichomonas* from the vagina, reaching a cure rate of up to 90%. Currently there's no evidence that supports its use in pregnant asymptomatic women, as there seems to be no reduction in preterm birth or improve low birthweight even as it clears the infection [2], [12] (LoE 1a; GoR A). However, in pregnant symptomatic women on one hand we have the adverse outcomes from the disease itself (which were already mentioned, on top of the facilitation of HIV transmission), while on the other hand one trial [13] presented an increased tendency towards preterm birth and low birthweight in the intervention arm compared to the control arm (LoE 1b). The association of infection with preterm delivery and preterm rupture of fetal membranes is well established [14]. Thus, the Cochrane metaanalysis [11] deemed that this findings were difficult to explain and unknown how real they would or wouldn't be, given that co-infections or other conditions might've been missed (LoE 1a; GoR A).

The treatment of choice for *Trichomonas* is metronidazole, taken orally at 500 mg twice a day for 5–7 days, with alternate regimens being orally in one 2 g dose or as vaginal ovulae at night for 5 days [2], [14] (LoE 1a; GoR A).

Any sexual partners should be treated simultaneously and sex should be avoided for a week after treatment has been completed. Test of cure is recommended if symptomatology remains [2] (GoR C).

### 3.3 Herpes

Genital herpes is caused by the Herpes simplex virus (HSV) type 1 or type 2 (globally the latter is the most common), enveloped enviroins with a double-stranded DNA core. In the USA, it's estimated to affect 1 out of 6 persons between the ages of 14–49, being twice as likely in women than in men [15] (LoE 3). HSV-1 is increasingly recognized as the etiologic agent of genital HSV infection, accounting for more than half of the new cases of genital HSV among teens and young adults [16] (LoE 3). Although most infections are asymptomatic, its classical clinical picture are typical lesions that are shallow, painful vesicles or ulcers of the genital or perianal area, along with malaise, myalgia, headache and lymphadenopathies in some cases. Symptomatic episodes resolve within 3 weeks. During the first year after infection, asymptomatic shedding and transmission can also happen. Afterwards the virus lies dormant in a dorsal root ganglion, reactivating variably, which leads to recurrent symptomatic episodes. Clinical diagnosis isn't sensitive or specific, but pregnant women who present with symptoms should undergo serologic testing (both IgG and IgM) and viral identification by culture, PCR or direct antibody fluorescence to identify the category and subtype of HSV infection [2], [15] (GoR C).

Neither the ACOG nor the CDC recommend routine screening of asymptomatic women for HSV during pregnancy [17] (LoE 4; GoR A). However, prevention of transmission of herpes infection from the male partner to the susceptible pregnant woman can decrease the incidence of neonatal herpes around 60–80% [18] (LoE 1b). Thus, it would be thought that the first step to prevent neonatal herpes would be determination of the susceptibility of the couple. Additionally, in a study that examined sexual behavior modifications in pregnancy after HSV serologic testing [19], it was concluded that pregnant women known at risk of HSV-2 acquisition by partner were up to 80% less likely to engage in unprotected sex than those with negative or not tested partners (LoE 1b).

Primary infection in a pregnant mother can cause miscarriage, preterm delivery, low birth weight and neonatal herpes. Although neonatal herpes is uncommon (with an estimated rate of 1:3,200 deliveries), it comes with a significant morbimortality [2], [15], [20] (LoE 2b). The majority of the neonatal herpes cases happen as direct contact with maternal secretions at birth, although postnatal infection can happen with contact with oral herpes. Congenital transplacental transmission is quite rare, accounting for less than 5% of the cases [2], [20].

Neonatal herpes can be classified into localized, encephalitic or disseminated [20]. Localized herpes (also known as SEM, or skin, eye and/or mouth disease), presents in the day 10–12 of life as a vesicular rash and infection confined to skin, eye and/or mouth, with no involvement of visceral organs or CNS. Encephalitic herpes (also known as CNS disease) accounts for 1/3 of the cases as seizures, lethargy, irritability, failure to thrive, temperature instability and bulging fontanelle. Between 60–70% will have skin lesions, as well, and generally it will present around 16–19 days of life. Finally, Disseminated disease accounts for 25% of the cases, presenting around day 10–12 of life with viral sepsis, respiratory failure and disseminated intravascular coagulation. Two-thirds of the cases with disseminated disease will also have concurrent encephalitis as well.

Vertical transmission is highest following primary infections on pregnancy (50%), mainly during the third trimester, as viral shedding will continue throughout delivery. At this point, there's exposure to the virus in the birth canal at a moment in which the newborn doesn't have protective transplacental maternal

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antibodies yet. Due to this, current prevention strategies for neonatal herpes are Cesarean section as well as suppressive treatment with acyclovir. Cesarean section performed before rupture of the membranes is estimated to decrease the likelihood of transmission by at least 60%, is advised from 34 weeks onwards in all cases with lesions suspected for primoinfection or in recurrent cases with lesions or prodromal symptoms [14], [15], [20], [21], [22] (LoE 4; GoR B). Although prophylactic acyclovir should be continued until delivery, HSV-infected pregnant women should be informed that although antiviral therapy and cesarean delivery can modify risk factors for neonatal HSV infection, no intervention could possibly eliminate completely the risk of transmission of HSV (LoE 4; GoR C).

On the other hand, even though nearly 15% of women with recurrent herpes will present lesions at the time of delivery, 1% will have asymptomatic shedding at delivery, which leads to a low estimated transmission rate, ranging from 0–4% [2], [14], [20] (LoE 3). This is why it's believed that the majority of women with recurrent infection are at a very low risk of delivering a baby with neonatal herpes, which isn't the case for those presenting with primary infection [23]. With this reasoning in mind, vaginal delivery is recommended in recurrent cases (GoR B).

In the most recent analysis of the Acyclovir in Pregnancy Registry, no apparent side effects were ascribed to it, for which treatment of symptomatic women to reduce the symptoms is warranted [14] (LoE 3). It is important to mention that acyclovir, famcyclovir and valacyclovir (the two last being antivirals that can also be used during pregnancy) are currently classified as category B, with an increasing amount of evidence suggesting that the benefits of suppressive therapy outweigh potential risks to the fetus [23]. The use of antivirals as suppressive therapy can be debatable, given that subclinical viral shedding is not entirely suppressed and neonatal HSV disease has been reported in infants with mothers that were receiving therapy [20]. However, treatment has been advised from 36 weeks both in the USA and in the UK, at a dosage of 400 mg three times a day, making its use widely accepted and applied [14], [15], [20] (GoR B). Treatment should be continued for 7–10 days or until lesions disappear in a Primary infection, or for 5 days in recurrent disease, while analgesia with acetaminophen, NSAIDs or opioids can help with symptomatic control [15].

There has been significant evidence as proof that HSV infection has increased rates of HIV co-infection and transmission, with patients with HSV being 2–4 times more likely to acquire HIV [15] (LoE 2a). As well, women with HSV and HIV co-infection have increased rates of intrapartum HIV transmission [15] (LoE 2a). Even then, two large randomized controlled trials [24], [25] concluded that prophylaxis with HSV suppressive therapy doesn't decrease transmission of HIV (LoE 1b).

### 3.4 Chlamydia

*Chlamydia trachomatis* is an obligate intracellular parasite that most commonly infects the cervix, followed by urethra, throat and rectum. Although 85% are asymptomatic, some may present with postcoital bleeding, lower abdominal pain, purulent vaginal discharge, cervicitis proctitis or dysuria [2]. Some complications from it include Pelvic Inflammatory Disease, ectopic pregnancy, tubal factor infertility and chronic pain.

Some adverse effects during and after pregnancy are abortion, premature rupture of membranes, ectopic pregnancy, low birth weight at pregnancy and maternal sepsis as well as conjunctivitis, pneumonitis or otitis media in the newborn [2], [26]. Around 50% of neonates born to women with untreated Chlamydia will present ophthalmia neonatorum and 15% pneumonitis [2] (LoE 3). The detection of specific antibodies against this pathogens helps to distinguish if a patient has been in contact or if there's an active infection.

In a study performed in 110 pregnant women in Mexico, it was noted that there's a high prevalence (77%) during pregnancy of anti-Chlamydiaceae antibodies, including *C. trachomatis*, *C. pneumoniae* and *C. psittaci* [26] (LoE 2a). The latter two organisms have been respectively associated to an increased risk for preeclampsia and for increased morbimortality for the mother and the fetus due to sepsis and abortion.

There are no reported randomized trials regarding screening for chlamydial infection during pregnancy [27]. However, there's evidence that screening and treating high-risk pregnant women can reduce the rate of adverse outcomes during pregnancy [27] (LoE 3; GoR B). As well, it has been proven that the rates of ectopic pregnancies and pelvic inflammatory disease are reduced in communities after screening for chlamydial infection was adopted [27] (LoE 3; GoR B).

HIV-exposed infants born to women with *N. gonorrhoeae* and *C. trachomatis* dual infection presented an

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increased mortality during the first 6 months of life when compared to only *C. trachomatis* or *N. gonorrhoeae*. As well, low birth weight infants were present in 42.9% of the cases with dual infection, while 28.6% had premature infants (LoE 3).

In a meta-analysis regarding treatment for Chlamydia during pregnancy, it was concluded that oral amoxicillin was as effective as erythromycin [28] (LoE 1a; GoR A). However, erythromycin has been proven to be slightly less efficient than azithromycin [14], in addition to it being a 7-day regimen that depends entirely on compliance from the patient (GoR A). Another study [29] proved that prevalence of *Chlamydia trachomatis* in patients who were previously prescribed erythromycin was the same as in patients without such treatment history. The suspicion was that multiple factors were the causes of the low treatment effect, amongst them the complexity of the regimen, lack of partner notification and lack of sexual abstinence (which can lead to reinfection) until both partners have been treated (LoE 3). It is suggested to avoid all sex with current partners until a week after the patient and the partner have finished treatment [2] (GoR C).

Current suggested treatment schemes during pregnancy are as follows: Azithromycin 1 g orally only dose; Erythromycin 500 mg orally 4 times a day for 7 days, or Amoxicillin 500 mg orally 3 times a day for 7 days [2], [27] (LoE 4; GoR A). Both doxycycline and ofloxacin are contraindicated in pregnancy [2]. Even though the efficiency of azithromycin is nearly absolute, a test of cure is suggested due to reduced efficacy of treatment in pregnancy or reinfection (GoR C). Both amoxicillin and erythromycin also add the non-compliance factor [2], [14]. If complaints or symptoms of urethritis or cervicitis persist, the patient should be retested for Chlamydia, Gonorrhea, Trichomonas and HIV, and reinfection or concomitant infection might have happened.

### 3.5 Gonorrhea

*Neisseria gonorrhoeae* is a gram-negative intracellular diplococcus whose primary site of infection in most commonly the endocervix, but can also present in the urethra, rectum, pharynx and conjunctiva. Although the symptomatology is similar to that of Chlamydia, Gonorrhea can be asymptomatic in up to 50% of cases [2]. Complications due to lack of treatment can be Pelvic Inflammatory Disease, hematogenous dissemination, skin lesions, arthralgia, arthritis and tenosynovitis.

Complications in pregnancy can also be quite severe, as infection by *Neisseria gonorrhoeae* during pregnancy brings a 4-fold increase in the risk of preterm delivery, as well as other complications such as chorioamnionitis, fetal loss, premature rupture of membranes, preterm labor and delivery [2], [14], [30] (LoE 3). Neonatal transmission happens in 30–50% of the cases, predisposing the infant to gonococcal ophthalmia neonatorum, reason for which prophylactic erythromycin ophthalmic ointment is prescribed at birth, regardless of mode of delivery [2], [30] (LoE 3).

As previously discussed, pregnant mothers with HIV as well as dual infection by *N. gonorrhoeae* and *C. trachomatis*, present an increase in the infant's morbimortality during the first 6 months of life.

Its treatment depends of Penicillinase-producing *Neisseria gonorrhoeae* in the community, which has been reported to up to 10% of all strains (LoE 3). Although a single intramuscular dose of 125 mg of ceftriaxone is sufficient to treat uncomplicated gonorrhea, the risk of preterm birth and the 30% increased dispersion volume, which is present during pregnancy, a single dose of 250 mg is preferred (GoR A). Test of cure can be performed after 4 weeks, with extended partner treatment and retreatment should be performed (GoR C). As well, a single oral dose of 400 mg of Cefixime is considered safe during pregnancy and lactation [14]. In a study performed in sub-Saharan Africa, all patients who were prescribed a single intramuscular dose of ceftriaxone had the infection cleared in a follow up performed 5 weeks afterwards [29] (GoR A).

Given that there's a high risk of a possible co-infection with *Chlamydia trachomatis* in at least 25% of the cases, extra treatment with a single dose of 1 g of azithromycin is also recommended [2] (LoE 3; GoR A). This treatment has been widely adopted to delay the onset of widespread cephalosporin resistance, as simultaneous resistance to two different antimicrobial classes is thought to be less likely. Even though a 2 g single dose has high cure rates for both Gonorrhea and Chlamydia, its gastrointestinal side effects are significant, for which an alternative regimen of 1g Azithromycin combined with 400mg of Cefixime has also been suggested [14] (LoE 2b; GoR A). Partner notification and abstinence until 1 week after treatment has been finalized is also suggested, while test of cure is recommended in all cases, given the emergence of resistance to treatment (GoR C).

Although ofloxacin is efficient in the eradication of gonorrhea, it can cause maturation defects in the joint

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cartilage of the offspring of animals, for which it is contraindicated in pregnancy [2], [14]. Most recent data by the CDC requires constant evaluation of proper treatment due to emerging resistance to antibiotic regimens.

### 3.6 Bacterial vaginosis

The etiological agents of Bacterial Vaginosis are *Gardnerella vaginalis*, *Mycoplasma hominis*, *Ureaplasma urealyticum* and other anaerobic bacteria, which proliferate when there's an ecological imbalance in the vaginal flora associated to a suppressed immune response. Whether there is transmission (and the mode of transmission) or if there's a spontaneous bacterial proliferation due to the aforementioned imbalance, still remains an enigma [31]. Diagnosis is usually reached by fulfilling the Amsel criteria and by laboratory testing. As well, a quick and inexpensive test that is usually performed as screening is vaginal pH testing, while alternative methods such as quantification of the microbial flora through vaginal swab Gram stain, have presented high sensitivities and specificities (LoE 1b; GoR A) [32], [33].

Although preterm birth has a prevalence of 5–10%, being the most common perinatal cause of morbimortality in the world, an association between genital tract infection and preterm birth is well known (LoE 3). It is thought that the decreased numbers of peroxidase-producing lactobacilli present in bacterial vaginosis may play a role in the ascending infection, prostaglandin release and weakening of membranes that end on late miscarriage [33]. By itself, it is thought that bacterial stimulation of the biosynthesis of prostaglandins ends up in the initiation of labor [32]. This is the reasoning behind the increase of over two-fold in the risk of preterm delivery in patients with BV [34] (LoE 3). As well, in a multivariable stepwise regression analysis performed by Donders et al. [33], it was also proven that BV (especially when *G. vaginalis* or *Mycoplasma* sp. were cultured) had a 5-fold increase on the risk of spontaneous abortion and early pregnancy loss. Due to this, screening and treatment should be started even during the first trimester [14] (LoE 3; GoR B).

An antenatal lower genital tract infection screening and treatment program, including vaginal smears screening for bacterial vaginosis, *Trichomonas vaginalis* and *Candida* sp., followed by standard antibiotic treatment with a positive screening test, showed a significant reduction in preterm birth, low birth weight and very low birth weight preterm births [9] (LoE 2b; GoR B). The results from this intervention led to savings in costs associated with prematurity.

Given that in patients with BV a co-infection with *Trichomonas*, Chlamydia, Gonorrhea and HIV has been reported [14] (LoE 3), this has to be taken into account or the treatment will be suboptimal and might explain the lack in the prevention of pregnancy complications such as preterm birth even after successful treatment. Thus, BV and abnormal vaginal flora can be seen as markers that prompt further investigation to prevent complications in pregnancy. More on this regard will be discussed in the following paragraphs, more in particular, when discussing aerobic vaginitis.

Regarding treatment, Metronidazole can be used as a 2 g only dose, as 500 mg twice a day for 5 days or as 250 mg thrice daily for 5–7 days [14]. Although this last dosage is the one recommended by the Centers for Disease Control and Prevention, in order to minimize possible fetal side effects [35], the increased distribution volume, 15% treatment failure and high recurrence rate goes against decreased dose regimens during pregnancy (GoR A). Even though vaginal treatment is possible, oral treatment is a better suggestion given that the prevention of preterm birth is better with this type of treatment [14] (GoR A).

Although both metronidazole and clindamycin eradicate 85% of BV, there can be up to 40–80% of recurrences in the first 6 months [14], which can't be improved with treatment of the sexual partner, for which test of cure needs to be performed (LoE 3; GoR B). The addition of acidifying vaginal products and lactobacilli may also prevent recurrences after acute treatment [36].

### 3.7 Aerobic vaginitis

Aerobic vaginitis is a relatively newly recognized vaginal flora disorder, based in an alteration of the vaginal bacterial microflora, which is altered towards a predominance of aerobes (such as *E. coli*, as well as *Klebsiella pneumoniae*, GBS and *S. aureus*). Along with this, there's also an increase in the localized inflammatory reaction and immune response. These findings are against the anaerobic flora and the suppressed immune response that is more characteristic of Bacterial vaginosis.

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In a similar manner to the Nugent score for BV, the microscopic diagnosis of AV is based on the following criteria: lactobacillary grades (LBG); number of leukocytes; proportion of toxic leukocytes; background flora and proportion of parabasal epitheliocytes [37]. Due to the fact that the diagnosis is only reached through wet-mount microscopy (which is not commonly performed by doctors worldwide), this remains an under-recognized disease.

The clinical picture is that of a red, inflamed vaginal mucosa with yellowish sticky discharge, pH above 6 and unpleasant (yet not fishy-like) odor. However, although such a presentation is rarely found in pregnancy, much less severe forms might actually be more frequent [38]. In pregnant patient who also present AV, an increase in the local production of IL-1, IL-6 and IL-8 happens, along with an increase of enzymatic activity that leads to preterm contractions and intrauterine infection [37], [38].

Although there has been no identifiable association between BV in labor and subsequent preterm birth, there is a strong and consistent association between preterm birth with the presence of *Klebsiella* sp., *E. coli*, *Staphylococci* and *Streptococci* [38]. This could be the reason why treatment with oral or vaginal metronidazole, which has no effect to anaerobic bacteria whatsoever, reduces BV in pregnancy but doesn't decrease the risk of PPRM or preterm birth [39] (LoE 3).

The best possible treatment for AV (either for pregnant or for non pregnant women) is yet unknown, given that previous trials have been focused on pregnant women with BV, and not with AV, from which the conclusions were either a lack of decrease in the preterm birth rate or even an increase in the risk of preterm birth, after completing a treatment with metronidazole [37] (LoE 3). Topical kanamycin in non-pregnant women with AV seemed to be a successful approach for Enterobacteriaceae [40], yet there have been no such trials in pregnant women. Although in theory, non-absorbable antibiotics might induce a favorable anti-inflammatory environment, the effects on pregnancy and on the fetus are yet to be found out. As well, given that there's an important inflammatory component, which includes parabasal cells and leukocytes, there's the thought that antibiotics may not be sufficient.

### 3.8 Chorioamnionitis

Definition of chorioamnionitis is through the presence of an active infection in the amniotic sac that causes inflammatory changes in the mother. Although there's evidence suggesting that bacterial proliferation may not be the initiating event to cause chorioamnionitis, this disease is traditionally considered as a polymicrobial process, with Mycoplasma and Group B Streptococcus (GBS), being significant contributors in the burden of this disease [41], [42], [43]. Its prevalence in developing countries is of 1–4% of pregnancies, with a likely higher rate in developing nations. Maternal bacteremia typically happens in 5–10% of the cases [44].

Ascending microbial invasion from the lower genital tract seems to be the most common pathway for intra-amniotic infection [45]. It is postulated that the mucus plugs is a functional and anatomical barrier to ascending infection during pregnancy, on top of which it has been supposed that the decidua is sterile during pregnancy [46].

Clinically, intrapartum fever warrants consideration of a potential diagnosis of chorioamnionitis, and it's considered the most predictive clinical sign that correlates to pathology [47]. Other signs and symptoms related to this disease are uterine tenderness, maternal and/or fetal tachycardia and purulent amniotic fluid. One option to confirm diagnosis is through amniotic fluid sampling and culture, although the invasive nature of the procedure limits its use [44]. On the other hand, histopathologic diagnosis is considered the gold-standard [43], [47], as it avoids some of the subjectivity of clinical diagnosis. That being said, its clinical utility is limited as the results may not be available until after delivery and as there's a high prevalence of histopathologic chorioamnionitis in asymptomatic mothers or neonates [48], [49].

As previously mentioned, the two most common bacteria associated to chorioamnionitis are Mycoplasma and GBS. On top of them, other microorganisms associated with this disease are Enterobacteriaceae, *S. aureus*, *G. vaginalis*, *N. gonorrhoeae* and *C. trachomatis* [43]. GBS has been controlled with the development of consensus guidelines and universal standardized screening, which has led to a dramatic reduction in neonates affected by GBS and should be followed in order to continue this decrease in the morbimortality [50] (LoE 4; GOR A). Such screening algorithms and use of intrapartum prophylaxis, recommended laboratory testing for colonization and the procedures for collecting and processing the clinical specimens are beyond the scope of this chapter and are readily available through the CDC [50].

Both maternal and neonatal mortality is difficult to assess, as in both cases it can present with an increase in morbidity due to complications, which in turn can potentially lead to death. Treating a patient

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promptly enough to avoid complications can be a conundrum for the clinician, given that current recommendations are to not treat patients at risk for chorioamnionitis, but instead to reserve antibiotic treatment until the point in which clinical chorioamnionitis is diagnosed [51] (LoE 4; GoR A). IV antibiotics are the preferred line of treatment, with a combination of ampicillin, gentamycin and clindamycin, or a single piperacillin-tazobactam being the recommended schemes. Even though oral clindamycin might not reduce the rate of histologic chorioamnionitis, PO antibiotics should be considered if IV antibiotics aren't available [52] (LoE 1b; GoR A).

Regarding management of preterm premature rupture of membranes (PPROM), 2 days of IV antibiotics followed by 5 days of oral antibiotics increases the latency between PPRM and delivery [43], [51]. The use of antibiotics beyond this scheme can be associated with no clinical benefit and worse neonatal outcomes [1] (LoE 1b; GoR A).

Even when antibiotic therapy can avoid temporarily the complications of chorioamnionitis, an extended latency period can lead to maternal sepsis, for which delivery should be considered under this diagnosis. Induction and labor should be started, avoiding cesarean delivery [43]. Even then, intra-amniotic infection can increase the likelihood of labor abnormalities, leading to a rise of 2 to 3 times in the risk of cesarean section, as well as an increase in the risk of pelvic abscess, wound infection and postpartum hemorrhage [53]. Maternal sepsis is quite uncommon in this setting, happening in less than 10% of the cases, with more serious complications like septic shock, adult respiratory distress syndrome, disseminated intravascular coagulation and maternal death being extremely unusual [53].

### 3.9 Group A streptococcus

Group A streptococci (GAS) infection has presented a reemergence since the 1980s, totaling more than 75,000 worldwide deaths every year. Its incidence in industrialized nations, which is higher during winter and spring, is of 6 for every 100,000 [54]. It has been proven that postpartum patients have 20 times higher incidence of GAS disease when compared to non-pregnant women [54], [55], [56] (LoE 2), which is in part theorized due to the fact that GAS can survive and grow in human amniotic fluid, despite its poor nutritional content, which can increase the risk of postpartum infection [57] (LoE 2b).

Although GAS vaginal carriage is less common when compared to GBS [58], it can cause a variety of diseases, ranging from mild pharyngitis, impetigo and puerperal fever, up to necrotizing fasciitis and streptococcal toxic shock syndrome (STSS), that can ultimately have a rapid clinical evolution and a mortality of up to 60%, if an infection that develops into STSS happens within 4 days of delivery. STSS can complicate the clinical course of around 20% of GAS infection-positive patients [54], [55], [56]. In 1993, the Working Group on Severe Streptococcal Infections defined STSS with two criteria (LoE 4). The first criterion is a group A streptococcal isolate from a sterile site (blood, CSF, pleural, surgical wound, etc.) or from a non-sterile site (vagina, superficial skin lesion, throat, etc.), while the second criterion is clinical signs of severity (hypotension of  $\leq 90$  mm Hg) with two or more of the following: renal impairment, coagulopathy, liver involvement, adult respiratory distress syndrome, generalized erythematous macular rash or soft-tissue necrosis [59].

Despite the high morbimortality, there are no recommendations for screening of pregnant women before delivery given that there's a low reported incidence of group A streptococcal genital tract colonization in pregnancy (0.03–0.27%), and there's a lack of proof that such colonization has a relationship with an increased risk of postpartum infection. As when, there's a lack of evidence that chemoprophylaxis is effective [35], [54] (LoE 4; GoR C).

This disease can present with a prodrome based on an upper respiratory tract infection, followed by few and non-specific symptoms (fever, nausea, vomit, abdominal pain, diarrhea, malaise and myalgia). If unattended and with a clinical course evolving into necrotizing fasciitis, there is severe pain out of proportion with the clinical findings. Even though there's a biochemical and hematological scoring system (Laboratory Risk Indicator for Necrotizing Fasciitis score), that can help with the prompt recognition of such complication, this method hasn't been evaluated widely and it doesn't delay surgical removal of the infected tissue (LoE 3; GoR C) [59], [62].

The first line of treatment for GAS is penicillin, which is most effective when administered early or after a low organism inoculum. If the administration is late or if there's a high inoculum, clindamycin is the better treatment option. In the setting of severe GAS infections, NF and STSS, penicillin and clindamycin should be given in combination (LoE 3; GoR B) [59], [60], [63], [64].

Other adjuvant therapies have been proposed in the setting of GAS infection. One of them is intravenous

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immune globulin G (IVIG), with only one randomized, double blind, placebo-controlled trial, which was terminated prematurely due to slow patient recruitment. In it, the placebo group's mortality rate was a 3.6 times higher, while the IVIG group had increased plasma-neutralizing activity against superantigens. That being said, no result achieved statistical significance [65], for which the benefit against the cost should be pondered in a case to case scenario. Intensive care with renal, cardiac and ventilation support might also be necessary in some cases, even suggesting hyperbaric oxygen therapy. However, due to obvious reasons, no randomized controlled trials have been conducted up to this point (GoR C).

### 3.10 HPV

Human papillomavirus is the most common sexually transmitted infection in the USA, with nearly 6.2 million new cases per year [35] (LoE 3). Although there are over 100 genotypes, they can be divided by their morbimortality into non-oncogenic and oncogenic. The former, or low-risk HPV (such as HPV 6 or 11), can cause low grade abnormalities of the cervix, anogenital warts or respiratory papillomatosis; while the latter, or high-risk HPV (including types 16 and 18), can cause intraepithelial neoplasia of the anogenital region, as well as anal and oropharyngeal cancers.

Although its prevalence is calculated to up to 30% of women between 20–30 years of age [14], this number in pregnant women ranges from 5.5 to 65% [66] (LoE 3). Analyzing data from the ATHENA trial [67] (LoE 3), out of the different genotypes, HPV16 is recognized as the most prevalent in all age groups, ranging from 3.5% to 0.8% in women aged 25–29 and ≥30 years, respectively. It also gave the greatest absolute risk of ≥CIN3 in women aged 25–29 and ≥30 years, by 14.2% and 15.1%, respectively. On the other hand, HPV18 was responsible for 50% of adenocarcinoma in situ (AIS) and 50% of invasive cancer cases. Due to the importance of both genotypes, identification of non-16/18 genotypes as a pool confers enough information as a possible screening tool.

The main direct effect on pregnancy is a statistically significant association between infections by HR-HPV and abortion, with genotypes 16 and 18 presenting P values of 0.009 and 0.012, respectively [68] (LoE 1b). Even though parity and HR-HPV infection are well known risk factors for cervical cancer, there is no association between pregnancy and HPV or LSIL [69] (LoE 1b). Vertical transmission is widely known to happen, with manifestations in the infant as condyloma acuminatum, oral lesions (verrucae, papillomas, condylomas and focal epithelial hyperplasia), and rarely as juvenile onset recurrent respiratory papillomatosis (JORRP). Most cases of vertical transmission occur at birth, followed by indirect exposure of the newborn to HPV on contaminated surfaces, or postnatally by the mother or caregivers (horizontal transmission) [70]. HPV-16 is the most frequently detected HPV genotype in pregnant women and newborns [70], [71], [72] (LoE 3).

Vertical transmission is demonstrated if the HPV type from the mother and the infant are concordant, with suspicion of intrauterine transmission only in a close maternal-newborn concordance [70], [73], [74]. Transmission rates of 5–72% are found in women with clinical evidence of HPV or detectable HPV DNA at delivery, decreasing to 1–18% if there's no such evidence (LoE 3). A meta-analysis of 9 prospective cohort studies [75] presented a pooled rate of transmission of 6.5% (range 1.5–46.6%), and a pooled relative risk (RR) of 4.8. When comparing vaginal delivery against cesarean delivery, the RR for HPV transmission was of 18% in the former against 8% in the latter (LoE 1a; GoR A).

Another study [72] confirmed that the risk of vertical transmission of HPV genotypes is relatively low, with both vertical and horizontal transmissions being demonstrated. 19.7% of infants born to HPV-positive mothers and 16.9% of those born to HPV-negative mothers were positive at up to 24 months of age at the last point of follow up (LoE 3).

Regarding vaccination, there are currently 3 different vaccines against HPV available in the market: Cervarix™ (bivalent; against types 16 and 18), Gardasil™ (quadrivalent; against types 6, 11, 16 and 18) and Gardasil 9™ (nonavalent; against types 6, 11, 16, 18, 31, 33, 45, 52 and 58). The first one was approved in 2006, while the last one was approved by the FDA in December 2014, this one with the potential to prevent 90% of cervical, vulvar, vaginal, anal and penile cancers [76].

Millions of doses have been given since its introduction to the market. As such vaccine is performed in young, fertile women, inadvertent administration during pregnancy has been performed. Even though HPV vaccination in pregnancy isn't recommended as per the ACOG [77], pregnancy testing also isn't mandatory before vaccination and the only recommended intervention in cases of accidental vaccination is to postpone further dosages until after delivery and contact the manufacturer. In a pooled analysis [78] of 11 studies, the incidence of serious adverse effects was quantified in females that received at least one dose of the bivalent or quadrivalent vaccines. No study found a statistically significant increase in the

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rate of spontaneous abortion, and no increased risk of major birth defects or fetal death associated with vaccines was demonstrated. The only parameter that had statistical significance was cesarean section ( $P=0.015$ ), with both the vaccinated and unvaccinated groups undergoing this procedure due to failure to progress, dystocia, repeat or elective procedure. Thus, it is concluded that there is little or no evidence found to demonstrate a correlation between vaccination and adverse outcomes of pregnancy, emphasizing that the true safety of vaccination in pregnancy hasn't been formally established by a randomized controlled trial (LoE 3).

Therapy is aimed at removal of the condilomata and not at definite treatment of the HPV infection. It should be noted that some treatments for precancerous lesions (such as cold-knife conization and loop excision) are associated with adverse pregnancy outcomes, such as cervical insufficiency, preterm delivery, low birthweight and perinatal death [79] (LoE 3). During pregnancy, treatment is limited to LASER or cryotherapy, although 30% aceto-acetate can also be used [14]. Both podophillin and podophillotoxin are contraindicated due to fetal neurotoxicity [14]. Finally, Imiquimod is not licensed for use during pregnancy.

## 4 Further research

There are multiple lines of research that can be extrapolated from the different lines of research that were written in this chapter, and which will be mentioned in the following paragraphs.

Regarding *T. vaginalis*, the question remains if the adverse effect of increased preterm birth in treated asymptomatic women with Trichomonas observed in one, prematurely stopped trial is real. As well, further randomized controlled trials are needed to determine the effects of antenatal infection screening and treatment programs in different contexts (different gestational ages, types of infection screening, and populations).

There are discrepant associations between bacterial vaginosis and preterm birth that can be found in recent studies, and they could potentially be explained in variations to the immunological response to BV. Priority should be given to a study analyzing the vaginal inflammatory response to microbial colonization, which takes into account genetic polymorphism in the cytokine response, in order to assess if this makes women more or less susceptible to BV and the implications this has to the risk of preterm birth. As well, even though there's no evidence that supports a "screen and treat" policy for BV and for AV, it would be interesting to reevaluate this possibility.

On the other hand, aerobic vaginitis offers a very ample amount of terrain for research to be performed. Initially, it would be interesting to compare data on pregnant women with aerobic vaginitis against those women who are colonized by coliforms or GBS, without presenting the clinical picture of AV. The optimal treatment for AV during pregnancy should have priority, given that this is a relatively newly identified disease and the implications it can have on pregnancy.

There are current efforts to develop a maternal vaccine for GBS, with the theory that a prepartum application may confer neonatal protection, even when there may be GBS transmission during breastfeeding [80], [81]. Its implementation might be cost-effective according to a study performed in South Africa, with prevention of the morbimortality of the disease both in developed and developing countries [81].

Particularities of HPV/HIV co-infection and the effect of HAART on HPV are still poorly understood. As well, the viral persistence with HIV infection in the setting of HPV co-infection should also be analyzed.

Further research into novel antimicrobial/contraceptive methods that could potentially be widely distributed in developing countries could change the perspective of STIs and pregnancy (or as an isolated finding). Female-based contraception/antimicrobial devices can also potentially cause a dramatic shift in the decision-making at the time of initiating sexual intercourse.

Given the high prevalence of HSV, as well as its shift from HSV-2 to HSV-1 in genital infections, it should be interesting that more studies are performed in order to clarify the association between HSV and HIV transmission. Also on this subject, even as maternal antiviral suppressive therapy decreases the incidence of genital recurrences at labor, it is questionable the extent in which these drugs actually prevent neonatal acquisition. Finally, the vaccine against HSV is still within an area of development, with no real vaccine that can be sufficiently effective as a preventive measure against infection by HSV-1 or HSV-2.

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## 5 Conclusions

Genital infections during pregnancy represent a significant risk to the mother and the child. Clinicians should consider that a pregnancy in the setting of a STI increases the probability of presenting complications that can increase importantly the complications for the mother and the fetus or newborn. Even though multiple studies involving different pathogens have proven that the susceptibility to acquire a second infection increases after contracting the first STI, the effects on pregnancy of two or more pathogens are well known to be or significantly worse.

Ideally, a patient should undergo a thorough medical history in order to assess the risk to contract an STI. Women at high risk should undergo all necessary measures in order to present an uneventful pregnancy, decreasing as much as possible the possibility of contracting a genital infection previous or during pregnancy, as well as controlling all variables to avoid transmitting an infection to their child.

It is of utmost importance the timely testing, diagnosis and management of STIs in pregnancy. It's also remarkable that treatment regimens can differ in pregnancy. This has an influence as the rate of success of the treatment sometimes is hindered by an increased dosage that in turn can cause poor tolerance and compliance by the patient. Thus, simplified treatment regimens are common in multiple genital infections during pregnancy.

Partner notification and treatment, risk reduction advice (such as to avoid sex while undergoing treatment), testing for other STIs and test of cure have to be taken into account and performed when required. As well, it was shown that the impact that these pathologies have on the mode of delivery depends entirely on the timing and type of infection, in relation to pregnancy gestation.

Finally, research into the epidemiological trends and resistance patterns needs to continue in a regular basis, in order to understand better the shifts that are happening in the pathophysiology of the disease and to offer good clinical practice guidelines. It can also be concluded that there are multiple areas of opportunity for research and development of new modes of protection against STI acquisition and transmission, like the vaccine against HSV and the mixed contraceptive/antimicrobial vaginal ring. Both of which were discussed in this chapter. Further research into novel treatment methods can vastly improve the current expected outcome of these diseases, and thus the morbimortality that they present at this stage.

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## 7 Conflict of interest

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