Herpes Simplex Virus A Practical Guide to Diagnosis, Management, and Patient Counseling for the Primary Care Clinician



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KEYWORDS

• Herpes simplex virus (HSV) • HSV diagnosis • HSV treatment • HSV counseling

KEY POINTS

- Genital herpes is a very common sexually transmitted infection caused by herpes simplex virus (HSV)-1 or HSV-2.
- Counseling is an important aspect of the management of genital herpes.
- Transmission occurs via sexual contact; the virus can also be transmitted from mother to child during pregnancy or delivery resulting in neonatal herpes infection.
- Molecular virologic tests performed on lesions are the preferred mode of diagnosis. Serologic testing can be considered in selected cases based on the clinical scenario.
- Options for treatment of genital herpes include acyclovir, valacyclovir, and famciclovir. The duration of therapy for primary infection is longer than for recurrent outbreaks. Suppressive therapy can be used to decrease frequency of outbreaks and decrease risk of transmission.

INTRODUCTION

Genital herpes is a chronic, lifelong sexually transmitted viral infection, which can cause recurrent, self-limited genital ulcers. It is caused by herpes simplex virus (HSV) type 1 and type 2 viruses. HSV-1 can cause both oral and genital infection but is mostly associated with oral lesions (herpes labialis). HSV-2 is the leading cause of genital ulcer disease and increases risk for HIV acquisition two- to threefold.¹ Although it can cause oral lesions in rare instances, HSV-2 almost exclusively causes genital infections and is more commonly associated with recurrent outbreaks.^{2,3} Most of the people infected with genital herpes are unaware of their status.⁴ A National

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Health and Nutrition Examination Survey (NHANES) found that only around 13% of HSV-2 seropositive individuals had been diagnosed with genital herpes.⁵ However, these individuals can still shed virus intermittently. Genital HSV is commonly encountered by primary care clinicians. Here, the authors review epidemiology, diagnosis, and management of genital herpes, illustrated by clinical vignettes and focusing on common patient questions.

Vignette 1: Transmission of Herpes Simplex Virus

A 19-year-old man presents to his primary care provider (PCP)'s office for follow-up after receiving a new diagnosis of genital HSV-1 infection, which was confirmed via type-specific nucleic acid amplification test (NAAT) of penile lesions. He does not understand how he could have acquired genital herpes because he and his female partner are monogamous and have never engaged in vaginal-penile contact. They do engage in condomless oral sex, and he notes that his partner intermittently has oral "cold sores." What is the most likely explanation?

HERPES SIMPLEX VIRUS-1 AND -2 PREVALENCE/INCIDENCE AND TRANSMISSION

Genital herpes is a common infection. In 2016, an estimated 3.7 billion people (~66.6% of the world's population under the age of 50 years) have HSV-1 infection at any site. One hundred ninety-two million people ages 15 to 49 years (prevalence of 5.2%) had genital HSV-1 infection, which accounts for ~30% of all genital infections. In addition, an estimated 491 million people (~13% of the world's population ages 15–49 years) have HSV-2 infection.⁶ In the United States, Spicknall and colleagues used HSV-2 seroprevalence data from the NHANES and the American Community Survey data to obtain recent estimates. In the United States, in 2018, it was estimated that there were 572,000 incident and 18.6 million prevalent genital herpes infections.⁷ However, an increasing numbers of genital infections are caused by HSV-1, so the prevalence is likely higher.⁸

Both HSV-1 and HSV-2 are transmitted through sexual contact (skin and mucosal surfaces). HSV-1 can be transmitted through oral or genital sex to the partner's oral or genital areas. HSV-2 is generally transmitted from genital tract to genital tract, although genital-oral transmission occurs in rare instances. Oral HSV-1 infection does not protect against HSV-2 acquisition, but does decrease the risk for symptomatic primary genital HSV-2 infection.⁹ HSV-2 infection protects against HSV-1 acquisition.¹⁰ Because individuals can shed HSV even when asymptomatic, a significant proportion of transmission may occur from asymptomatic partners.

Vignette 1 Follow-Up: It Is Possible the Patient in Vignette 1 Could Have Acquired Genital Herpes Simplex Virus-1 from Oral-Penile Contact with His Partner

Neonatal HSV transmission happens when HSV-1 or HSV-2 exposure occurs in utero, peripartum, or postpartum. Approximately 5% of neonatal HSV is accounted for by in utero transmission. Peripartum transmission is the most common route for neonatal HSV infection. Postpartum infection occurs when the infant is exposed to orolabial or cutaneous lesions.¹¹ The highest risk for transmission to the neonate occurs when primary HSV infection occurs during pregnancy.¹² The risk of transmission from mother to infant is 30% to 50% in women who acquire genital herpes near the time of delivery, compared with less than 1% in women with prenatal history of recurrent genital herpes or who acquire genital herpes in the first half of pregnancy.^{12,13}

Vignette 2: Clinical Manifestations and Diagnosis of Herpes Simplex Virus Infection

A 23-year-old woman comes to her PCP's office for evaluation because she has been having significant vaginal/vulvar pain and dysuria accompanied by subjective fever and malaise for the past 3 days. She denies prior history of similar symptoms. She reports a new male partner in the last month and reports condomless receptive vaginal sex. She denies oral or anal sex. On examination, she has multiple painful shallow erosions over part of the vagina and vulva. What tests should be obtained?

CLINICAL MANIFESTATIONS OF HERPES SIMPLEX VIRUS Primary Infection

Clinical manifestations usually occur within a week of exposure. Genital symptoms classically include painful lesions but can also include dysuria, pruritus, vaginal or urethral discharge, and painful inguinal lymphadenopathy.¹⁴ Typically, lesions start as papules or vesicles which spread rapidly over the genital area and may coalesce into larger areas of ulceration. Crusting occurs on non-mucosal surfaces, but not on mucosal surfaces.¹⁵ Genital lesions can be unilateral or bilateral and may be extensive. In addition, systemic symptoms may occur early in the course of primary infection, including fever, headache, malaise, and myalgias.^{14,15} The resolution of genital lesions occurs within 2 to 3 weeks even without antiviral therapy.¹⁴

Primary HSV infection can also result in urethritis, cervicitis, vulvovaginitis, and proctitis. Symptoms of urethritis associated with HSV include dysuria, meatitis, urethral discharge, and lymphadenopathy. However, in approximately 30% of cases, genital lesions are not present.^{16,17} HSV-associated cervicitis is characterized by areas of focal or diffuse friability, erythema, erosive, and ulcerative lesions on the cervix with or without external herpetic lesions.¹⁵ Primary herpes in the vagina can lead to extensive swelling, discharge, and severe dysuria. Some individuals with severe primary genital herpes outbreaks can develop urinary retention secondary to sacral radiculopathy. This is an uncommon complication, which is usually self-limited, but may require bladder catheterization until it resolves.^{15,18} HSV-associated proctitis can present with rectal pain, bloody and/or mucoid discharge, and tenesmus.^{15,19,20} In addition, HSV proctitis can be associated with systemic symptoms including fever, malaise, and myalgia.¹⁵ Anal ulcerations are present in a minority of individuals.²⁰

Meningitis and encephalitis are rare but may be associated with HSV infection. HSV-1 is more commonly associated with encephalitis, whereas HSV-2 is more commonly associated with meningitis.²¹ HSV-2 is also associated with benign recurrent lymphocytic meningitis (Mollaret meningitis), which is characterized by recurrent episodes of meningitis which last 3 to 7 days and resolved without neurologic sequelae.¹⁶

Recurrent Infection

Typically, recurrent outbreaks are milder than primary infections and are heralded by a prodrome. Prodromal symptoms include burning and tingling and precede lesion development by approximately 24 hours. Lesions in recurrences are usually unilateral and fewer when compared with the primary infection.¹⁴ Genital lesions resolve within 1 to 2 weeks even without antiviral therapy. Recurrence frequency varies widely and is more common in HSV-2 infections compared with HSV-1 infections.³ Typically, recurrences are more frequent during the first year after infection and decline over time.²²

Infection During Pregnancy/Neonatal Infection

Global estimates of neonatal herpes infection incidence are 10 cases/100,000 live births.²³ Rarely, infection during pregnancy has been associated with fulminant

maternal hepatitis.¹⁰ Neonatal herpes presents within 1 to 3 weeks after birth. Clinical manifestations of neonatal HSV include localized skin, eye, and mucous membrane disease (45%); central nervous system (CNS) disease (30%); and disseminated disease (25%).²⁴ Skin, eye and mucous membrane disease presents as vesicles and ulcers. Systemic symptoms are similar in skin, eye, and mucous membrane disease and CNS disease, which include lethargy, poor oral intake, irritability, and temperature instability. CNS disease may cause seizures. Approximately two-thirds of infants with CNS disease will have cutaneous lesions.¹¹ Disseminated disease presents as sepsis syndrome, respiratory distress/failure, severe liver dysfunction/failure, and disseminated intravascular coagulopathy.²⁵ Despite advances in diagnosis, treatment, and prevention, neonatal HSV infection continues to cause significant morbidity and mortality. Without antiviral therapy, mortality rate is estimated at 60%.²⁶ With antiviral therapy, mortality rate is estimated at 60%.²⁶ With antiviral therapy, mortality rates have been reported at 6% to 8% (**Box 1**).^{25,27}

DIAGNOSIS OF GENITAL HERPES SIMPLEX VIRUS

Clinical diagnosis of genital herpes can be challenging as the classic lesions associated with genital herpes may have resolved or be resolving at the time of evaluation. However, if genital lesions are present at any stage, type-specific virologic testing ideally by NAAT should be performed to confirm clinical diagnosis.

Virologic Tests

HSV NAAT assays and HSV cultures can be performed on samples collected from cutaneous or mucocutaneous lesions. If vesicles or pustules are present, lesions should be unroofed and the base of the ulcer swabbed to obtain adequate cells.²⁸ HSV culture is generally available, but the sensitivity can be fourfold lower than HSV NAATs particularly if lesions are old and viral load is low.²⁹ NAATs are highly sensitive and specific and are the preferred method of testing.³⁰

Serology

Serologic tests assess for antibodies to HSV. The utilization and interpretation of serologic tests for genital herpes depends on the clinical scenario. Evaluation should include history and physical examination followed by choice of appropriate diagnostic testing. The diagnosis of genital herpes by using only type-specific antibody tests can be problematic. HSV immunoglobulin M (IgM) antibodies do not distinguish between primary infection and recurrent infections and are advised against.^{31,32} There are

Box 1

Differential Diagnosis of Genital Ulcers

- Syphilis (caused by Treponema pallidum)
- Chancroid (caused by Haemophilus ducreyi)
- Granuloma inguinale (caused by Klebsiella granulomatis)
- Lymphogranuloma venereum (caused by Chlamydia trachomatis serovars L1–3)
- Epstein–Barr virus
- Mpox
- Beçhet disease
- Neoplasm
- Trauma

several type-specific immunoglobulin G (IgG) assays that are commercially available for use. The type-specific IgG assays have sensitivity between 80% and 98%. Both false-negative and false-positive tests can occur. False-negative testing more frequently occur in early infection, so if there is concern for recent acquisition, repeat testing with type-specific antibody assays can be performed approximately 12 weeks following presumed time of exposure.^{33–35} False-positive enzyme immunoassays occur at low index values (<3.0).³⁶ There is poor specificity at low index values, so confirmatory testing with a second method (ie, Western blot) should be performed before interpretation and may improve accuracy.³² If confirmatory testing is not available, patients need to be counseled on the limitations of serologic testing and providers must be aware that false-positive tests occur.

HSV type-specific serologic testing is not recommended for:

- Screening in the general population^{4,37}
- Routine screening of asymptomatic pregnant women³⁸
- HSV-1 serologic screening for the diagnosis of genital HSV-1. Ideally, genital HSV-1 infection should be diagnosed by use of virologic testing (NAAT or culture).^{4,39}

HSV type-specific serologic assays can be considered for:⁴

- Recurrent or atypical genital symptoms or lesions with negative virologic testing
- Clinical diagnosis of genital herpes without laboratory confirmation
- A patient whose partner was diagnosed with genital herpes.

Vignette 2 Follow-up: Primary genital HSV infection should be suspected in this patient

The following test specific to herpes should be sent: HSV NAAT from swabs from the vaginal or vulvar lesions. Additional workup might include screening for other STIs, including HIV, syphilis, gonorrhea, chlamydia.

Vignette 3: Herpes Simplex Virus Recurrence and Prevention

A 28-year-old woman has had three outbreaks of genital HSV-2 infection in the last year. She has not been sexually active for over a year. These episodes are quite painful and cause significant disruption to her life. She is wondering what her options are to manage or reduce these episodes as well as to prevent transmission to future partners. How would you counsel her?

MANAGEMENT AND TREATMENT

Acyclovir, valacyclovir, and famciclovir are approved to treat and suppress genital herpes and prevent transmission. All of these medications have excellent safety profiles.⁴⁰ There is no cure for genital herpes, but the use of antiviral medications decreases the duration of symptoms and viral shedding in both initial infection and recurrence.^{41,42} **Table 1** outlines the recommended treatment regimens for genital herpes for the general population, people living with HIV, and pregnant people. Treatment of first episode should be started empirically and continued for 7 to 10 days.⁴ For treatment of recurrences, dosing is higher and duration is shorter.^{4,43} Antivirals should be started during the prodrome in recurrences for best outcomes.

Recurrence rates are decreased by 70% to 80% with suppressive therapy, which also reduces HSV-2 transmission among heterosexual serodiscordant partners, and should be discussed with all patients with symptomatic HSV-2 infection.^{10,44–48} It should be noted that the data are limited with regard to decreasing transmission in asymptomatic patients with genital HSV-2 infection.⁴ Patients

Table 1 Recommended regimens for treatment and suppression of genital herpes				
	General Population	People Living with HIV	Pregnant People	
Initial infection therapy ^a				
Acyclovir	400 mg PO 3 times/day for 7–10 d	400 mg PO 3 times/day for 7–10 d	400 mg PO 3 times/day for 7–10 d	
Valacyclovir	1 g PO 2 times/day for 7–10 d	1g PO 2 times/day for 7–10 d	1 g PO 2 times/day for 7–10 d	
Famciclovir	250 mg PO 3 times/day for 7–10 d	250 mg PO 3 times/day for 7–10 d		
Episodic therapy	1			
Acyclovir	800 mg PO 2 times/day for 5 d OR 800 mg PO 3 times/ day for 2 d	400 mg PO 3 times/day for 5–10 d	400 mg PO 3 times/day for 5 d OR 800 mg PO 2 times/ day for 5 d	
Valacyclovir	500 mg PO 2 times/day for 3 d OR 1g PO daily for 5 d	1 g PO 2 times/day for 5–10 d	500 mg PO 2 times/day for 3 d OR 1 g PO daily for 5 d	
Famciclovir	1 g PO 2 times/day for 1 d OR 500 mg PO once, followed by 250 mg 2 times/day for 2 d OR 125 mg PO 2 times/ day for 5 d	500 mg PO 2 times/day for 5–10 d		
Suppressive therapy ^b				
Acyclovir	400 mg PO 2 times/day	400–800 mg PO 2–3 times/day	400 mg PO 3 times/day	
Valacyclovir	500 mg PO daily ^c OR 1g PO daily	500 mg PO 2 times/day	500 mg PO 2 times/day	
Famciclovir	250 mg PO 2 times/day	500 mg PO 2 times/day		

^a Treatment can be extended if healing is incomplete after 10 days of therapy.

^b In pregnant people, suppressive therapy is recommended starting at 36 wk gestation.

^c Valacyclovir 500 mg daily may be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (ie, \geq 10 episodes/year).

Source: Based on CDC STI Treatment Guidelines (https://www.cdc.gov/std/treatment-guidelines/) and Adapted from Table 1 in Van Wagoner et al. Inf Dis Clin North Am 2023.

should be counseled on the potential for breakthrough lesions and viral shedding.⁴⁹ The continued use of suppressive therapy should be revisited periodically.¹⁰

Treatment in Pregnancy

All pregnant people should be asked about history of genital herpes or genital signs or symptoms concerning for genital herpes during their pregnancy and at the time of delivery. If no signs or symptoms of genital herpes, vaginal delivery is acceptable. However, if active genital lesions are present at the time of delivery, cesarean delivery is recommended to decrease the risk for neonatal HSV infection.^{4,13} Acyclovir is safe in pregnancy and breastfeeding and is recommended for use in pregnant people for first episode and recurrent episodes of genital herpes.^{4,50,51} For pregnant people with known history of genital herpes, the use of suppressive therapy starting at 36 weeks gestation decreased the risk for recurrent episodes of genital herpes, although break through cases of neonatal herpes have been reported.^{52,53} For pregnant people who acquire HSV during pregnancy, empirical antiviral therapy is recommended while awaiting confirmation, and then, suppressive antiviral therapy is recommended starting at 36 weeks if infection occurs early in pregnancy.⁴

Treatment in People Living with Human Immunodeficiency Virus

Antiretroviral therapy (ART) and immune reconstitution are major elements of genital herpes management. Even with immune reconstitution and ART, recurrences are more frequent in people living with human immunodeficiency virus (HIV) (PLWH). In PLWH with low CD4 counts on initiation of ART (<200 cells/mm³), frequency of recurrences increases in the first 6 months.¹⁰ Treatment is similar to other populations, although dose and duration are increased.⁴ Suppressive therapy does not reduce the risk for HIV or HSV-2 transmission in coinfected people.^{54,55}

PREVENTION

There are limited options for prevention of genital herpes transmission to partners in addition to suppressive therapy. Compared with no condoms, consistent and correct condom use resulted in a 30% decreased risk of HSV-2 acquisition.⁵⁶ In another study, it was found that HSV-2 transmission protection from condom use was different by sex. Correct condom use decreased the per-act transmission risk from cis-men to cis-women by 96% and from cis-women to cis-men by 65%.⁵⁷ There are no data on impact of condom use for prevention in anal sex. In addition, there is ongoing research on developing preventive and therapeutic vaccines for prevention of transmission, but currently there is no effective vaccine available.¹⁰

Vignette 3 Follow-Up

This patient has two available options for management of the frequent outbreaks: episodic or suppressive therapy. Given frequency of the outbreaks and reported significant pain associated with outbreaks, suppressive therapy may be more beneficial to the patient if she is willing to take daily medication. Continued need for suppressive therapy should be reassessed periodically.

COUNSELING

Genital herpes is quite stigmatized, and patients are often distressed on receiving the diagnosis.^{58,59} Patients may feel shame, guilt, or anger; distress regarding transmission; fear of partner reactions; and difficulty in disclosing status.⁶⁰ Providing counseling to the individual with genital herpes and their sex partners is an important part of the management of genital herpes.⁴ The major goals of counseling include helping the patient understand the infection, options for treatment, access resources for information, and prevent sexual and perinatal transmission.^{4,60}

Counseling discordant couples is particularly challenging, especially in case of committed relationships where the (cis-gender) female partner is uninfected and where future pregnancy is desired. Despite the effectiveness of suppressive treatment, avoiding sex during outbreaks, and condom use, transmission may still occur over the long term. Moreover, couples may feel that such preventive measures will interfere with their (sexual) relationship and may decide to let "nature runs its course," knowing that for the female partner, infection occurring before pregnancy is preferable over infection occurring during pregnancy, especially during the second half. An open discussion of pros and cons should be the basis of a shared decision-making process. Regardless, infection status should be determined in the early phases of pregnancy of

Table 2 Common herpes simplex virus-related patient questions/concerns: summary of counseling points ^a			
Patient Question/Concern	Counseling Points		
What causes genital herpes?	 Caused by a virus There are two types of HSV (HSV-1 and HSV-2) Both types can cause genital herpes It is a common condition No cure, the virus persists in the body (latent state) 		
I have never been diagnosed with an STI or HIV. I do not have any symptoms currently, nor do I have a history of any previous or recurrent genital symptoms. None of my sexual partners have had STIs that I know of. I am not pregnant. I want to get routine STI screening "just to be safe." Should I be tested for HSV?	 Routine screening for HSV in asymptomatic individuals is not recommended for most people Routine screening for other STIs generally includes testing for HIV, gonorrhea, chlamydia, and syphilis It is important to screen for gonorrhea and chlamydia at sites that are exposed during sex 		
How did I get genital herpes?	 Transmission occurs through skin-to-skin or mucous membrane contact Transmission can occur even when a person is asymptomatic 		
Can I get genital herpes through oral sex?	 Genital HSV-1 infection can occur from receiving oral sex from a partner who has oral herpes (HSV-1) Genital HSV-2 infection can occur through oral sex, although is rare 		
My partner and I have had other sexual partners in the past but have been in a monogamous relationship for the past 8 mo. I have just had an episode of genital ulcers for the first time and was diagnosed with genital herpes. Does this mean my partner has definitely had other partners in the past 8 mo they are not telling me about?	 Many people infected with genital herpes are unaware of their status Intermittent viral shedding can occur in asymptomatic individuals Transmission may occur from asymptomatic individual who may be unaware of their status Current diagnostics do not allow for determination of timing of infection 		
If I have HSV 1 can I get HSV 2 (and vice versa)?	 You can have both HSV-1 and HSV-2 Oral HSV-1 infection does not protect against HSV-2 acquisition Oral HSV-1 does decrease the risk for symptomatic primary genital HSV-2 infection HSV-2 infection does protect against HSV-1 acquisition 		
I have just been diagnosed with HSV—who do I need to tell?	 Last sexual partner, current partner, and future partners should be told. Current partners should be informed and receive testing. 		
	(continued on next page)		

Table 2 (continued)			
Patient Question/Concern	Counseling Points		
How can I avoid giving my future partners HSV?	 Avoid sex during prodrome/outbreak Condoms reduce but do not eliminate transmission Suppressive therapy reduces but does not eliminate transmission Risk for transmission increases during outbreaks Individuals with genital herpes can have healthy sex lives 		
I am worried about how my partner will react to the news of my HSV diagnosis—what _ can I do?	 Support group availability Individual or couples counseling 		
I feel very guilty and ashamed about this diagnosis—what can I do?	 Sex is normal and important part of life Genital herpes is very common Suppressive therapy helps decrease frequency of outbreaks Support groups are available 		
Does having HSV mean I cannot get pregnant or that if I do it will harm the baby?	 Fertility not affected Does not prevent an individual from having children Routine screening for HSV not recommended during pregnancy If partner is known to have genital herpes and pregnant person has no known history of genital herpes, type-specific serologic tests for the pregnant person can be helpful for counseling Suppressive therapy starting at 36 wk gestation decreases risk of viral shedding during delivery in those with recurrent genital herpes 		
I am pregnant at 14 wk, I do not have a known history of HSV but my male partner has a history of genital HSV outbreaks. What should I do?	 Highest risk for neonatal herpes is when a woman becomes infected late in pregnancy Women with no history of genital herpes should abstain from sex with partners known or suspected to have genital herpes in the third trimester Women with no known history of orolabial herpes should abstain from receptive oral sex with partners known to have or suspected to have orolabial herpes in the third trimester. Type-specific serologic tests can be useful for guiding counseling (see above). 		
Other concerns	 Genital herpes is a manageable condition Treatment of outbreaks with safe and effective antivirals Genital herpes does not cause cancer Genital herpes can increase risk for acquiring HIV infection (counseling on pre-exposure prophylaxis (PrEP)) 		

^a See also Table 2 in Van Wagoner et al. Inf Dis Clin North Am 2023.

any woman in a discordant relationship to prevent the possibility of vertical transmission and its devastating sequelae.

Table 2 outlines the key points to address with regard to frequently encountered patient concerns/questions. The Centers for Disease Control and Prevention and the Canadian Government have resources for counseling tools.^{4,60}

SUMMARY

Genital HSV infection is a very prevalent STI, which causes self-limited, recurrent genital ulcers. Treatment decreases duration of symptoms and signs and can be provided as episodic or suppressive therapy. Genital herpes can have a substantial impact during pregnancy and on sexual health in general. Counseling on natural history, transmission, treatment, and management of sexual partners is an integral part of management of genital herpes.

CLINICS CARE POINTS

- Nucleic acid amplification tests (NAATs) are more sensitive than culture and are the preferred method of testing for individuals with genital lesions.
- Type-specific serologic assays (IgG) can be used in certain clinical scenarios but are not recommended for screening in the general population.
- Clinical manifestations in primary infection can include genital and systemic symptoms and signs and are generally more severe than recurrent episodes.
- Antiviral therapy decreases duration of clinical manifestations and viral shedding. Suppressive therapy can decrease frequency of recurrences and reduce the risk of transmission.
- In pregnant people, acyclovir and valacyclovir should be used to treat first-episode and recurrences. Suppressive therapy with acyclovir is recommended starting at 36 weeks gestation to reduce recurrences at delivery.
- Counseling is an important aspect of the management of genital herpes as genital herpes is stigmatized and can cause substantial distress for patients.

DISCLOSURE

T.A. Batteiger and C.A. Rietmeijer have no disclosures.

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