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Genital Herpes: Gynaecological Aspects

This guideline has been reviewed by the Infectious Disease Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: The purpose of this guideline is to provide recommendations to gynaecology health care providers on optimal management of genital herpes.

Outcomes: More effective prevention of complications and transmission of genital herpes.

Evidence: Medline was searched for articles published in French and English related to genital herpes and gynaecology. Additional articles were identified through the references of these articles. All study types and recommendation reports were reviewed.

Key Words: HSV, genital herpes, antiviral, prevention, screening, counselling

Recommendations

1. Up to 70% of all genital HSV-2 infections are transmitted during asymptomatic shedding; therefore, the use of condoms is recommended to lessen the likelihood of disease transmission. (II-A)
2. A laboratory-based diagnosis of genital herpes is essential for its effective management. (II-A)
3. Suppressive treatment is suggested for patients who have
   - at least 6 recurrences per year
   - significant complications, but fewer than 6 recurrences per year
   - their quality of life significantly affected
   - social and sexual dysfunction
   - to lower the risk of transmission to a sexual partner or fetus/neonate. (II-B)
4. The use of the anti-viral valacyclovir, coupled with condoms and safer sex counselling, is recommended for individuals with proven genital herpes. (I-B)
5. Routine or targeted HSV screening is not indicated. (III-B)

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INTRODUCTION

Better laboratory tests and epidemiological studies have allowed us to understand that genital herpes is a significant sexual and reproductive health problem and public health issue. The purpose of this document is to review the pathophysiology, epidemiology, risk factors, modes of transmission, clinical presentation, laboratory diagnosis, antiviral treatment, and prevention of transmission. The SOGC clinical practice guideline, Management of Herpes Simplex Virus in Pregnancy,[1] provides recommendations for management of HSV in obstetrical practice. The recommendations in this guideline are evaluated using the criteria of the Canadian Task Force on Preventive Health Care (Table 1).[2]

PATHOPHYSIOLOGY

Herpes simplex infection is usually acquired by mucosal surface contact with a person excreting the virus. It is a member of the *Herpesviridae* family. It has a double stranded

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of Evidence Assessment*	Classification of Recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[2]
†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.[2]

DNA. It causes infection in sensory nerves and establishes latency in the regional dorsal root or sensory ganglion. From there, it can reactivate and travel down the axon to the mucosal or epidermal surface, where it can shed or cause clinical manifestations. The cause for viral reactivation is not well understood. There are two types of HSV, HSV-1 and HSV-2, distinguished by their surface glycoprotein (gD). Recurrent genital HSV is most commonly due to HSV-2, but at least 10% is due to HSV-1.[3] However, there are increasing rates of primary genital HSV that are due to HSV-1 and that recur rarely.

EPIDEMIOLOGY

Genital infections caused by Herpes simplex viruses types 1 and 2 (HSV-1 and HSV-2) are the most frequent cause of genital ulcerations.[4] In industrialized countries, the prevalence rate for HSV-2 infection in adults is up to 20%. Canadian data show that HSV seroprevalence in women of reproductive age is 17% and that it increases with age. It is estimated that there are 50 000 new cases of genital HSV in Canada per year (approximately 137 cases each day). In a subset of people with more than 10 lifetime partners, the rate of genital herpes was 50%.[5] Prevalence of HSV is higher in women infected with HIV.[6]

ABBREVIATIONS

HIV	human immunodeficiency virus
HSV	herpes simplex virus
NAAT	nucleic acid amplification techniques
PCR	polymerase chain reaction
STI	sexually transmitted infection

RISK FACTORS

According to a US study, risk factors for having genital herpes infection,(HSV-2 primarily) include higher number of sexual partners, a prior history of any sexually transmitted infection, including HIV, a history of a genital lesion in self or partner, non-Caucasian race, female gender, increasing age, and low socioeconomic status.[7]

MODES OF TRANSMISSION

Transmission predominantly occurs during anogenital contact. Some transmission occurs during oro-genital contact. Infections transmitted from the mouth to the anogenital area are usually type 1. Type 2 infection is rarely transmitted from the anogenital area to the mouth. An infection by one type at one mucosal site does not protect against acquisition at another mucosal site, but the signs and symptoms are then much less severe. Type 1 infection does not confer full protection against type 2 but may lessen the signs and symptoms of acquisition of infection at the new mucosal site. Transmission from an infected mother to her baby can occur rarely transplacentally, during labour and delivery, or after birth from indirect contact with the mother's infected secretions. Detailed discussion of this can be found in the companion article on herpes in pregnancy.[1]

Table 2. Clinical manifestations and serostatus

Clinical manifestations	Serostatus at time of acquisition
Primary infection	HSV-1 and HSV-2 negative
Non-primary 1st episode	HSV-1 or HSV-2 positive and lesions with contrary antibodies to virus
Recurrent	HSV-1 and/or HSV-2 seropositive
Asymptomatic shedding	HSV-1 and /or HSV-2 seropositive

Up to 70% of all genital HSV-2 infections are transmitted during asymptomatic shedding (see recurrent disease in clinical presentation section). Condoms may be useful to lessen the likelihood of transmission.

CLINICAL PRESENTATION

HSV infection can be described by

- site: anogenital or orolabial
- stage of infection: initial or recurrence
- prior immune status: primary or non-primary (infection usually at another site).

See Table 2 for clinical manifestations and serostatus at time of acquisition.

Initial Infection

If the initial infection is primary, there can be both local and systemic manifestations. The systemic manifestations include flu-like symptoms (fever, headache, myalgia), difficulty in initiating urine or bowel movement, and genital pain. The genital manifestations of the initial infection vary from mild or unrecognized symptoms to severe bilateral, vesicular lesions, with an erythematous base. They evolve to pustules, which then ulcerate and finally form crusted lesions.[5] There can be more than one generation of lesions in a primary infection, representing absence of immunity to the virus rather than autoinoculation. Of note, severe bilateral manifestations are not exclusively associated with primary infection.[8]

Recurrent Infection

The spectrum of recurrent disease ranges from asymptomatic viral shedding to overt clinical recurrences.

Asymptomatic Shedding

Asymptomatic shedding occurs when the individual has no lesions or symptoms, but virus is present on the surface of the skin or mucosa.[9]

Asymptomatic transmission is possible from those infected with either oral or genital herpes. Both HSV-1 and HSV-2 seropositivity usually represents oral/labial HSV-1 infection, and HSV-2 seropositivity represents urological and anogenital infection. Most importantly, infectiousness appears to be equivalent in individuals who are completely unaware of their disease and those that know they are infected.[10] It has been established that in the absence of symptoms, HSV-2 can be detected in the genital tract, by viral culture, on 3% of days for the first year after initial infection, and then on 1% of days for the next 2 years. If measured by nucleic amplification techniques, asymptomatic shedding can be as high as 30%. The relevance of shedding by PCR has been questioned, as this technique may also detect dead virus or levels of virus that are below an infectious threshold. Asymptomatic shedding is more frequent in a person with recent primary infection, near the time of clinical recurrences (before and after), and in immunocompromised people.[11,12] The majority of people infected with genital herpes will shed sporadically and unpredictably, regardless of whether they are symptomatic or not.[13,14]

Clinically Evident Lesions

Clinically evident lesions are preceded by a prodromal stage in 90.6% of patients in 59.1% of episodes.[15] During the prodromal stage, the virus is already present on the skin or mucosal surface.

Clinical Challenges in Dealing With Genital Herpes

STI principles

Patients coming for STI screening should be made aware that they are not screened for herpes. Diagnosis of recurrent genital herpes is a challenge since recurrences are short-lived, allowing a mean of less than 5 days to perform a viral culture. Most patients present to their health care provider for the first time during a recurrence, seeking a diagnosis. Up to one half of viral culture tests performed during a recurrence may come back as falsely negative, because of improper sampling techniques and improper specimen handling and transportation. PCR is more sensitive but not routinely available. It is now recognized that most people (91%) with genital herpes are unaware of their diagnosis. However, a large proportion (60–75%) are misdiagnosed with other urogenital conditions. Self-diagnosis of initial and recurrent HSV infections is frequent, although often

Table 3. Laboratory tests used for the diagnosis of HSV infection: interpretation of results[16]

Test used for genital herpes diagnosis	Interpretation	Comments
Viral identification test	Confirms HSV infection	Needs excretion of the virus at the site of swabbing
Viral culture	Confirms type 1 or type 2 infection	Short-lived excretion especially in recurrence
		Many false negative especially in recurrent infection
NAAT	Confirms type 1 or type 2 infection	Identifies non living HSV. May associate non herpetic lesions with HSV
Immunofluorescent staining	Confirms type 1 or type 2 infection	Lack sensitivity
		Many false negatives especially in recurrent infection
Tzanck test	Confirms herpes infection	Lack sensitivity and does not differentiate between herpes virus types
		Many false negatives especially in recurrent infection
Serology		
Type-specific	HSV-2+ and HSV-1– Indicates type 2 infection (probable genital)	Lack of accessibility
	HSV-2– and HSV-1+ Indicates type 1 infection (but not location, could be oral and/or genital infection)	
	HSV-2+ and HSV-1+ indicates dual infection, likely type 2 infection of the genital area and type 1 infection of the oral area	
	HSV-2– and HSV-1– if > 12 wks from infection, indicates absence of HSV infection	
Non-type-specific	If negative, confirms no HSV infection.	Does not differentiate types or dual infection of types if positive

mistaken. The signs and/or symptoms that lead women believe they have HSV often have other causes, including the following[16]:

- vaginitis
- allergies or reactions (toilet paper, sanitary napkins or other menstrual products, soaps, condoms, shaving instrument or hair removal product)
- sexual intercourse (lack of lubrication, too frequent sexual intercourse, vaginal dryness)
- irritation from tight jeans, thongs, bicycle seats
- urinary tract infections
- hemorrhoids or anal fissures

Inappropriate self-treatment is common, particularly with over-the-counter therapies that address the symptoms and not the infection. This may complicate the laboratory diagnosis and delay prevention of transmission or adequate treatment.

DIAGNOSIS OF HSV INFECTIONS

Necessity of a Confirmed Diagnosis

A laboratory-based diagnosis of genital herpes is essential for its effective management. It provides evidence of the etiology of the lesions to support education, partner notification, and counselling. Clinical diagnosis of HSV cannot be accurately based on history-taking and visual examination, because many lesions are atypical (false negative), and many other clinical entities mimic herpes (false positive).

The public health agency of Canada recommends that all diagnoses of genital herpes be confirmed by laboratory testing.[17]

Laboratory Tests

There are 2 categories of tests to diagnose HSV infections: (1) viral identification tests and (2) serologic tests. See Table 3 for interpretation of results.

Viral identification

There are two main types of viral identification tests: viral culture and NAAT. A viral identification test should be used for all patients who have not previously had a diagnosis of HSV. It should be performed on wet excreting lesions: vesicles, pustule, or wet ulcers. Both viral tests perform best with early lesions. Viral culture does not perform well when the ulcers are dried or in the presence of crusted lesions.

Type-specific serology test

Type-specific serological testing can be used as

- **a diagnostic tool**, when there is suspicion of clinical genital herpes, but viral identification tests cannot be performed or are negative. This may be useful in the following situations: for patients who find it hard to schedule visits; when transport of specimen or viral testing is not an option; for patients who have lesions infrequently; when viral identification tests performed on lesions thought to be genital herpes are negative; and for pregnant women with a history of undiagnosed urological or anogenital problem.
- **a case-management tool** in a clinically discordant couple or a pregnant woman to decrease risk of transmission to a susceptible partner or a baby; or to determine the susceptibility of a partner before an HSV-2-infected individual is prescribed valacyclovir prophylaxis to prevent transmission to the susceptible partner.

What tests should be ordered in patients?

- **In patients with lesions**, a viral identification test should be ordered. Cell culture, when available, represents a good test if sufficient virus is collected from the fluid of the lesions or if enough infected cells from the base of the ulcer are collected. NAAT, such as PCR, is preferred but may not be readily available. A negative viral identification test does not eliminate the possibility of a genital herpes diagnosis.
- **In patients without lesions**, if the situation is such that the patient cannot wait for another lesion to appear, a type-specific serology should be ordered.

Non-type-specific serology

Non-type-specific serology does not differentiate HSV type 1 from type 2 or dual infection. Non-type-specific serology can be useful only if negative, to confirm susceptibility.

Type-specific serology

HSV-2 seropositivity cannot technically confirm genital herpes, but it makes the diagnosis very likely if the patient had lesions in the appropriate dermatomes.

Both HSV-1 and HSV-2 seropositivity usually represent orolabial HSV-1 infection and HSV-2 urological or anogenital infection.

HSV-1 seropositivity in the presence of HSV-2 seronegativity makes the case difficult to interpret. In a patient without oral or genital lesion, this is more likely to represent an orolabial rather than a genital infection. But in a patient with a genital herpes-like lesion, the diagnosis of HSV-1 genital herpes is likely but should ideally be confirmed by a viral identification test when the lesion reappears.

TREATMENT

Antiviral Treatment[17]

Oral antiviral agents are effective in many ways for almost all HSV infected patients. These agents have a very strong safety record. Topical antiviral agents have limited efficacy in acute infections and no shown efficacy in genital recurrences and therefore are not recommended.

Initial episode

If an initial infection is suspected or diagnosed and the lesions have not fully crusted, then antiviral therapy is warranted to decrease the duration and severity of the outbreak.

In initial infections, one of the following should be administered:

- Acyclovir 200 mg orally 5 times a day for 10 days, or
- Acyclovir 400 mg orally 3 times a day for 10 days, or
- Famciclovir 250 mg orally 3 times a day for 5 days, or
- Valacyclovir 1000 mg orally twice a day for 10 days.

Recurrent infection

Both episodic and suppressive treatment regimens are available for patients with recurrent genital herpes. Treatment needs to be based on patient preferences and nature of disease. Public health indications suggest suppressive therapy to prevent transmission of the virus to others. The decision to use episodic or suppressive therapy should be shared between the patient and the care provider. There are times in an individual's life when one therapy may be more appropriate.

Episodic Treatment

Episodic treatment is patient initiated therapy that needs to be pre-prescribed so patients have medications available at the time of an outbreak. This may be recommended for patients who have infrequent lesions and a clear prodrome, and whose outbreaks have a minimal effect on their quality of life or social/sexual functioning:

Recommended antivirals should be given as soon as possible at the onset of prodrome to decrease the duration and severity of the outbreak.

Recommended regimens

- Acyclovir 200 mg orally five times a day for 5 days, or
- Acyclovir 800 mg orally three times a day for 2 days, or
- Famciclovir 125 mg orally twice a day for 5 days, or
- Famciclovir 1000 mg orally twice a day for 1 day, or
- Valacyclovir 500 mg orally twice a day for 3 days, or

• Valacyclovir 1.0 g orally once a day for 3 days.

Topical antiviral treatment has never been shown to be of any help in minimizing recurrences.

Suppressive Treatment

Suppressive treatment is suggested for patients having at least one of the following effects from their infection: significant problems with health-related quality of life; social and sexual dysfunction; a need to lower the risk of transmission to a sexual partner or fetus/neonate; significant complications with fewer than 6 recurrences per year; at least 6 recurrences per year. In addition, patients with recurrent genital HSV who have susceptible partners or who engage in sex with new or multiple partners should be offered suppressive therapy for the prevention of transmission to others. This recommendation is based on data from a valacyclovir suppression study in which the use of the antiviral valacyclovir coupled with condoms and safer sex counselling was shown to reduce the risk of sexual transmission by 48%. This effect was limited to the time of use. Efficacy was proportional to compliance. The rate of transmission was evaluated to be 1.1% for those taking at least 95% of their pills.[18]

Suppressive therapy consists of the following:

- Acyclovir 400 mg orally twice a day, or
- Acyclovir 200 mg three to five times a day, or
- Famciclovir 250 mg orally twice a day, or
- Valacyclovir
  - 500 mg orally once a day
  - 1 g orally once a day

The length of suppressive therapy is adjusted to the patient's needs. The prescription should be renewed yearly, and a revaluation of the patient's situation is recommended at this time. Suppressive dosing for pregnancy is specific.[1]

FUTURE CONSIDERATIONS

No therapeutic vaccine is available. Only one prophylactic vaccine is under phase 3 study and expected in the near future. This glycoprotein based prophylactic vaccine has been shown to give 74% protection for women seronegative for both HSV-1 and HSV-2.[19] Larger trials are in progress.

Prevention of Stigmatization

Sexually transmitted infections, including genital herpes, are frequently stigmatized and associated with negative feelings such as depressive mood, isolation, fear of rejection, and fear of being discovered, and with self-destructive behaviour.[20] Health care providers can help by referring the patients to psychologists or sexual medicine experts, and/or self-help groups. Stigmatization may prevent patients from accessing appropriate curative and preventive care.[21]

Disclosure of Status

If a new partner is told about genital herpes status, transmission is 50% less likely. Since median acquisition time occurs 61 days after initiation of intercourse with a new partner, efforts should be made for proper and timely disclosure of HSV status to ensure barrier methods are used, with or without antiviral protection. Most of those resisting disclosure fear rejection. They should be told that all potential sexual partners have the right to be informed before they consent to sexual activity, and they should be given advice on how to disclose their status.

CONCLUSION

Genital HSV infection is the most common urogenital ulcer disease in the world. Most patients who are HSV-2 seropositive should be considered undiagnosed, not asymptomatic. Laboratory confirmation is recommended before a diagnosis of genital herpes is issued. Antiviral therapy and personalized counselling help patients to adapt better to the challenges of genital herpes and help prevent transmission of infection.

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