

Guidelines for the Management of Herpes Simplex Virus in Pregnancy

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

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Disclosure statements have been received from all members of the committee.

Abstract

Objective: To provide recommendations for the management of genital herpes infection in women who want to get pregnant or are pregnant and for the management of genital herpes in pregnancy and strategies to prevent transmission to the infant.

Outcomes: More effective management of complications of genital herpes in pregnancy and prevention of transmission of genital herpes from mother to infant.

Evidence: Medline was searched for articles published in French or English related to genital herpes and pregnancy. Additional

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

articles were identified through the references of these articles. All study types and recommendation reports were reviewed.

Values: Recommendations were made according to the guidelines developed by the Canadian Task Force on Preventive Health Care.

Recommendations

1. Women's history of genital herpes should be evaluated early in pregnancy. (III-A)
2. Women with known recurrent genital herpes simplex virus (HSV) should be counselled about the risks of transmission of HSV to their neonates at delivery. (III-A)
3. At delivery, women with recurrent HSV should be offered a Caesarean section if there are prodromal symptoms or in the presence of a lesion suggestive of HSV. (II-2A)
4. Women with known recurrent genital HSV infection should be offered acyclovir or valacyclovir suppression at 36 weeks' gestation to decrease the risk of clinical lesions and viral shedding at the time of delivery and therefore decrease the need for Caesarean section. (I-A)
5. Women with primary genital herpes in the third trimester of pregnancy have a high risk of transmitting HSV to their neonates and should be counselled accordingly and should be offered a Caesarean section to decrease this risk. (II-3B)
6. A pregnant woman who does not have a history of HSV but who has had a partner with genital HSV should have type-specific serology testing to determine her risk of acquiring genital HSV in pregnancy before pregnancy or as early in pregnancy as possible. Testing should be repeated at 32 to 34 weeks' gestation. (III-B)

Validation: These guidelines have been reviewed and approved by the Infectious Diseases Committee of the SOGC.

Sponsor: The Society of Obstetricians and Gynaecologists of Canada

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INTRODUCTION

This document focuses on the prevention, diagnosis, and management of genital herpes in pregnancy and makes recommendations for the prevention of neonatal HSV disease. Gynaecologic aspects of HSV are addressed in SOGC Clinical Practice Guideline No. 207.¹

This document reflects emerging clinical and scientific advances on the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of these contents may be reproduced in any form without prior written permission of the SOGC.

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.⁴³

†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.⁴³

EPIDEMIOLOGY

HSV genital infection has been rising in prevalence in the developed world.² A Canadian study revealed that the age-adjusted rate of HSV-2 seropositivity in pregnant women is 17%, with a range of 7.1% to 28.1%.³ Neonatal HSV continues to be a dire medical consequence of genital herpes.⁴ Canadian neonatal HSV surveillance data show a rate of 1 in 17 000 live births. According to US data, the incidence of neonatal HSV is 1 in 3500 live births.⁵ This discrepancy may be due to underreporting of mild or unrecognized disease in surveillance studies.

DISEASE MANIFESTATIONS

Neonatal and Congenital HSV

Neonatal HSV refers to the acquisition of infection at or near the time of delivery through exposure to the virus from

the maternal genital tract. There are also rare cases of iatrogenic or familial transmission after birth from oral or other skin lesions. Neonatal herpes infection is diagnosed when the evidence for the HSV infection manifests more than 48 hours after delivery. It is helpful to make the distinction between neonatal and congenital HSV infection. Congenital infection is the very rare phenomenon of fetal acquisition of HSV in utero which is a form of TORCH infection.

Type of infection	Timing of acquisition	Mode of acquisition
Congenital	In utero (antepartum)	Transplacental
Neonatal	At or near birth (intrapartum)	Genital exposure
Neonatal	Postnatal (post partum)	Nosocomial (staff or family direct skin contact)

The manifestations of neonatal or congenital HSV infection have been classified into three levels of disease. These are

1. skin, eye, and mouth infection (rarely fatal; however, 38%⁶ may develop neurological disease as a sequela);
2. central nervous system disease (manifested as encephalitis with or without skin, eye, and mouth infection); and
3. disseminated disease (the most serious form of infection, which has a 90% mortality rate if untreated).⁷

A diagnosis of neonatal herpes infection can be made on the basis of clinical presentation and/or the presence of a positive culture from the neonate more than 48 hours after

ABBREVIATIONS

HIV	human immunodeficiency virus
HSV	herpes simplex virus
IUFD	intrauterine fetal death
IUGR	intrauterine growth restriction
NAAT	nucleic acid amplification techniques
PCR	polymerase chain reaction
STI	sexually transmitted infection
TORCH	toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex

delivery. In all cases of suspected neonatal or congenital HSV infection, an early consultation with a pediatrician or pediatric infectious diseases expert is highly recommended. Intravenous antiviral therapy (acyclovir) should be initiated as soon as possible as per standard dosing guidelines.⁸ There is evidence of significant reduction in mortality (from 58% to 16%) and neurologic sequelae with its use.⁹

Maternal HSV

Genital infection with HSV is more common with HSV-2, but primary HSV-1 is increasing in frequency^{10,11} and has been implicated in neonatal herpes infections more often in Canada.¹² Management of HSV in pregnancy requires an understanding of the clinical manifestations of the disease.¹

Clinical Manifestations of Genital Herpes

HSV infection can be described in 2 ways:

1. stage of infection: first clinically recognized episode of infection or recurrence;
2. prior immune status: primary or non-primary (infection usually at another site).

Primary infection occurs when the individual encounters either HSV-1 or HSV-2 and has no prior exposure (i.e., HSV-1 and HSV-2 antibody negative) to either viral type.

Non-primary first episode is the first clinically recognized episode, but the individual has HSV-1 or HSV-2 antibodies from a prior exposure.

Recurrent infection is clinically evident infection in an individual with antibodies to that virus.

First clinically recognized episode of infection

Determining the nature of the first clinically recognized episode is important for counselling in pregnancy. The implications for the mother and fetus/neonate are different depending on whether the infection is primary, first episode/non-primary, or the first recognition of recurrent disease.

The typical clinical manifestations include unilateral or bilateral vesicular lesions, with an erythematous base, located in the area of the sacral dermatome (usually S2, S3) and which can, therefore, be on the genital skin or adjacent areas. They often evolve into pustules, then ulcerations, and finally, if on keratinized skin, crusted lesions.¹³ Although this is the classic presentation, atypical presentations are common, including minor erythema, fissures, pruritus, and pain with minimal detectable signs. Of note, some individuals will never show clinical manifestations but can be demonstrated to be episodically shedding virus.

Genital herpes, whether from HSV-1 or HSV-2, can also be acquired in those previously orally infected by the other

HSV type. For example, an individual with HSV-1 of the orolabial area may acquire HSV-2 in the genital region.

Recurrent infection

Clinical presentation of recurrent infection varies from completely clinically unrecognized asymptomatic viral shedding to overt clinical recurrences.

Asymptomatic shedding

Asymptomatic shedding of HSV-2 and HSV-1 is possible from both the oral and genital area. 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, then on 1% of days for the next 2 years.¹⁴ Higher rates of viral DNA detection are described with PCR shedding data, but the relationship of this to infectivity is not well understood. Asymptomatic shedding is more frequent in a person with recent primary infection, near the time of clinical recurrences (before and after), and in immunocompromised persons.¹⁵ The majority of infected persons with genital herpes will shed sporadically and unpredictably regardless of whether they are symptomatic or not.¹⁴

Clinically evident lesions

Clinically evident lesions are preceded by a prodromal stage approximately 80% of the time. During this prodromal stage, the virus is already present on the skin or mucosal surface. Genital HSV-2 infection results in clinically evident recurrent disease more often than HSV-1.¹⁶

IMPLICATIONS OF GENITAL HSV IN PREGNANCY

Primary Infection in Pregnancy

The risk for neonatal infection seems to be greatest when maternal primary infection occurs in the third trimester. In this situation, the mother acquires infection but is unable to complete seroconversion to IgG prior to delivery, and the infant is delivered in the absence of protective passive IgG from the mother. In this case, there is a 30% to 50% risk of neonatal herpes infection.^{17,18}

Studies had suggested that primary infection occurring in the first or second trimester caused an increase in spontaneous abortion and/or prematurity and fetal growth restriction.^{19–21} However, more recent series have not confirmed these findings.¹⁷ In rare cases, there is transplacental transmission resulting in congenital (in utero) infection. This is typically very severe. The fetal manifestations include microcephaly, hepatosplenomegaly, IUGR, and IUFD.

Management of Maternal Primary HSV Infection

Treatment with antivirals, including during the first trimester of pregnancy, may be appropriate if maternal symptoms

are severe. There are enough data to support the safety of acyclovir throughout pregnancy, particularly when there are compelling reasons for maternal treatment.²²

Type-specific HSV serology in pregnancy could theoretically be used to determine whether a pregnant woman is at risk of HSV acquisition. However, the benefit of this strategy to prevent neonatal disease has not been proven. If an HSV discordant couple is identified (when the pregnant woman is seronegative and the partner is positive), advice should be given to decrease the risk of acquisition of primary HSV in pregnancy. Abstinence from both oral-anogenital and anogenital-anogenital contact is the most effective strategy to prevent HSV acquisition. Data gathered from non-pregnant patients support the use of suppressive antiviral therapy to decrease the risk of sexual transmission.²³ By extrapolating the data, antiviral suppression could be offered to the partner with genital HSV (in conjunction with condom use) in order to decrease the risk of transmission to the pregnant partner.

Mode of Delivery in Women With Primary HSV Infection

Primary infection with either type 1 or type 2 in the third trimester of pregnancy presents the highest risk (30–50%) to the infant, but there is little evidence to guide management. In these unusual cases, elective Caesarean section is recommended. If the first clinically recognized episode of HSV occurs in the third trimester or near delivery and determination of serostatus cannot be made, then managing the woman as if this was a primary infection is appropriate. Neonatal cultures for HSV should be performed following delivery, and the neonate should be observed carefully for signs of HSV infection. The prenatal care provider should ensure that the individual caring for the infant instructs the parents with respect to potential signs and symptoms of neonatal HSV disease.

Maternal Recurrent HSV in Pregnancy

A pregnant woman with herpes simplex infection who acquired the infection prior to pregnancy will have IgG antibodies to herpes simplex and will pass these to the fetus transplacentally. Presumably because of the protective passive antibodies, it is uncommon for a neonate to develop herpes infection from a mother with recurrent disease. However, if a genital HSV lesion is present at the time of vaginal birth, risk of neonatal infection is reported to be 2% to 5%.^{24,25} A woman with recurrent disease who does not have a lesion evident at delivery still has a small risk of asymptomatic shedding (approximately 1%), and therefore the risk of neonatal infection can be calculated to be 0.02% to 0.05%.^{25,26}

For women with recurrent outbreaks during pregnancy, antiviral therapy is not recommended prior to 36 weeks, but if manifestations are very severe and/or unacceptable to the woman, therapy can be individualized.

Published data from randomized controlled trials have shown that the use of suppressive antivirals starting at 36 weeks' gestation reduces the risk of viral shedding, clinical herpes lesions, and need for Caesarean section at the time of labour.²⁷ In addition, no infant in these studies acquired neonatal herpes, although the sample size cannot preclude a small failure rate.^{18,28–31} The dosages in these studies were acyclovir 400 mg, taken orally three times a day, or acyclovir 200 mg, taken four times a day, from 36 weeks until delivery. In addition, more recent data support the use of valacyclovir for suppression of genital herpes in late pregnancy, using a dosage of 500 mg orally twice daily.^{32,33} Valacyclovir is the valine ester of acyclovir and is broken down to acyclovir in the blood stream, so safety data on acyclovir may be extrapolated to valacyclovir. A recent study has demonstrated the cost effectiveness of acyclovir suppression in pregnant women.³⁴ Use of acyclovir in pregnancy has not been associated with any consistent pregnancy complications or fetal/neonatal adverse effects, other than transient neutropenia in data from the Acyclovir Pregnancy Registry.^{22,35,36} There is little information on the use of famciclovir in pregnancy. In the absence of more complete clinical safety data, acyclovir or valacyclovir would be preferred when HSV antiviral medication is indicated in pregnancy.

If preterm delivery is predicted in a woman with recurrent genital herpes, then use of suppressive antivirals may be considered at an earlier gestational age. If antiviral suppression is ineffective at preventing a lesion at the time of labour, management should be the same as for a lesion in the absence of antiviral therapy, i.e., a Caesarean section is recommended.

Mode of Delivery for Maternal Recurrent Genital Herpes

It is now clear that serial maternal antenatal cultures are not predictive of the development of neonatal herpes, and they are therefore not indicated.^{37,38}

Caesarean section is recommended if an HSV lesion or prodrome is present at the time of delivery. This is the case even if the lesions are remote from the vulvar area, such as on the buttocks or thighs, as there is still a risk for concurrent cervical or vaginal shedding of virus.^{39,40} For prevention of neonatal herpes, the Caesarean section should ideally be performed within four hours of rupture of membranes.⁴¹ If delivery is imminent, there is likely no benefit to Caesarean section. The protective effect of Caesarean

section has not been proved in the context of prolonged rupture of membranes with active genital herpes.

In the event of preterm premature rupture of membranes, where prolongation of pregnancy is preferable, then use of suppressive antiviral is recommended until delivery.

In management of delivery in women with a history of recurrent HSV, avoidance of scalp electrodes and fetal scalp sampling is recommended.⁵ Use of any intrauterine monitoring devices should be considered carefully.

POSTPARTUM CONSIDERATIONS

Any HSV lesions that appear in the mother post partum should be managed with proper hand washing and contact precautions. These precautions apply to all individuals who are in close contact with the infant.

Breast feeding is contraindicated only if the woman has active lesions on the breast.

Infection control issues are addressed in the Health Canada guidelines.⁴²

Recommendations

1. Women's history of genital herpes should be evaluated early in pregnancy. (III-A)
2. Women with known recurrent genital herpes simplex virus (HSV) should be counselled about the risks of transmission of HSV to their neonates at delivery. (III-A)
3. At delivery, women with recurrent HSV should be offered a Caesarean section if there are prodromal symptoms or in the presence of a lesion suggestive of HSV. (II-2A)
4. Women with known recurrent genital HSV infection should be offered acyclovir or valacyclovir suppression at 36 weeks' gestation to decrease the risk of clinical lesions and viral shedding at the time of delivery and therefore decrease the need for Caesarean section. (I-A)
5. Women with primary genital herpes in the third trimester of pregnancy have a high risk of transmitting HSV to their neonates and should be counselled accordingly and should be offered a Caesarean section to decrease this risk. (II-3B)
6. A pregnant woman who does not have a history of HSV but who has had a partner with genital HSV should have type-specific serology testing to determine her risk of acquiring genital HSV in pregnancy before pregnancy or as early in pregnancy as possible. Testing should be repeated at 32 to 34 weeks' gestation. (III-B)

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