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Management of Genital Herpes Simplex Virus Infection for the Pregnant Woman

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ABSTRACT

Given the prevalence of genital herpes simplex virus infection in childbearing women and the serious consequences of genital herpes transmission to the newborn during delivery, optimal management of genital herpes during pregnancy is justified. Prevention and health promotion, continuity of care and the participation of the woman and her partner in care are key elements for optimal management of the pregnant woman with genital herpes. Appropriate management of serodiscordant couples must include screening tests for the pregnant woman with a partner who is a HSV-2 carrier, proven diagnosis and individualized prenatal preventive measures. Optimising preventive measures should bring about a reduction of genital lesions at the time of delivery and consequently reduce the number of cases of neonatal herpes and of transfers of care from midwife to physician.

KEY WORDS

herpes simplex virus, midwife, prenatal care, prevention

This article has been peer reviewed.

The incidence of genital herpes simplex virus (HSV) infection has risen by 20 to 30% in industrialized countries in the last 20 years, women and young adults being the most affected.[1, 2] We distinguish between two serotypes of herpes simplex virus: HSV-1 and HSV-2. HSV-1 is essentially responsible for orolabial herpes and due to orogenital contacts can cause genital herpes.[3] Contrary to HSV-1, HSV-2 transmission occurs exclusively by sexual transmission from an individual that is excreting HSV-2 in the genital area.[3]

The epidemiology of genital herpes in Canada is not well known. Two population studies, one from Ontario the other from British-Columbia reported a seroprevalence of HSV-2 of 3.2 and 7.1 % respectively, for pregnant women between 15 and 19 years of age and of 23.1 and 28.2 % for those aged between 40 and 44.[4, 5] Although HSV-2 is presently responsible for the majority (60 to 80%) of genital herpes, the proportion of genital HSV-1 infections is on the rise, especially in women.[1] A study conducted in Nova-Scotia revealed that over half (58.1%) of the cases of primary genital herpes in women are attributable to HSV-1.[6]

Natural history of HSV infection

Primary oral HSV-1 infection

Primary oral HSV-1 infection, being the first mucosal or cutaneous contact with HSV that a person who is seronegative for HSV-1 and HSV-2, occurs most often by orolabial means during childhood from a subject having a history of labial herpes.[1,3,7]

Improved hygiene conditions in developed countries have brought about a regular reduction in the prevalence of orolabial HSV-1 herpes during childhood.[1] The practice of bucco-genital relations by young adults increases the risk of contracting a primary genital HSV-1 infection.[1, 8] For unknown reasons, HSV-2 oral infections are rare.[1,3]

Primary genital HSV infection

Primary genital HSV infection usually includes systemic symptoms (pyrexy, myalgia, headache), numerous vesicular or pustular lesions, then ulcerations and finally crusts. [3, 8, 10] Genital lesions are located in the perianal and cervicovaginal regions, and are accompanied by an often painful bilateral inguinal adenopathy.[11] The total length of this sequence is around three weeks, the length of contagion is of about 11 days. [10] The infection can also take on genital symptoms which are less specific (pruritus, erythema, fissures), atypical lesions located along the thighs and the lumbosacral region, present only prodomal symptoms or be totally asymptomatic. [3, 10, 12] Serious complications such as herpetic encephalitis and aseptic meningitis are observed in close to 16 to 26% of subjects. [13]

Non-primary initial genital infection

Non-primary initial genital infection, which also corresponds to the first genital contact with HSV, but with a subject who already has underlying HSV antibodies from a previous orolabial HSV-1 infection.[10] The characterization of the first clinically evident episode of a non-primary initial genital infection are intermediary between those of a primary genital infection and those of a recurrent infection.[10] Over half of primary genital infections and of non-primary initial genital HSV infections are asymptomatic or unknown.[12, 14] From 10 to 80% of the first clinically evident manifestations that bring the subject to consult a doctor are in fact a recurrent infection.[7]

Recurrent infection

Following the first genital contact with HSV, the infected subject will excrete HSV intermittently from the genital area, either asymptomatically or during clinical recurrences.[9] The clinical symptoms of a recurrent infection are less severe than those of a primary infection; the genital lesions are often unilateral and less numerous, affect to the cervix is less frequent, the excreted viral load is smaller and the duration is three times shorter. [10, 11] Prodomes not followed by legions are frequent in over 40 % of subjects and are often unknown. [9] The majority of infected subjects will have, on average, one to five recurrences per year during the two first years following the primary HSV infection.[15] The frequency of recurrences varies greatly, but it is estimated that it would be three times higher for a genital HSV-2 infection than for a HSV-1 infection and would diminish slightly over time. [12,16]

Asymptomatic virus shedding

Asymptomatic virus shedding is more frequent with HSV-2 in the year following primary genital infection, with women who have had over 12 recurrences a year and in the seven days preceding and following a recurrent infection. [12, 16]

Transmission

Over 60% of genital HSV infections are transmitted during periods of asymptomatic viral shedding. [3, 14] According to prospective studies with serodiscordant monogamous couples, the annual transmission rate of genital HSV-2 was between 3 and 4 % with a female source partner and 11 and 17 % with a male source partner.[18, 19, 20] The presence of HSV-1 antibody increases the risk of asymptomatic seroconversion, although more studies are necessary in order to determine if antibody reduces the risk of acquiring a genital HSV-2 infection. [12]

Transmission of the virus to the newborn occurs most frequently during childbirth (85%) and more rarely during the prenatal (5%) and postnatal periods (10%). [8, 10, 15] Exceptionally, primary genital HSV infection can cause a congenital HSV infection in the fœtus accompanied by microcephalia, hydrocephalus, chorioretinitis, vesicular skin legions. [11] It is at the time of delivery with the presence of a primary genital infection and with the absence of passive antibody transmission to the fœtus that the risk of transmission is the highest (50-80 %). [11,17,21] It is four times lower in the presence of a non-primary initial genital infection (20%) and considerably lower (2-8%) in the presence of a recurrent infection. [11, 17, 21] As numerous studies show, over half of the newborns infected with HSV, were contaminated by a woman with no known history of genital herpes. [22, 23, 24] The use of fœtal monitoring by electrodes on the scalp or any other procedure (forceps, vacuum extractor) that

can compromise the newborn's epidermal barrier are factors that could increase the risk of contracting a HSV infection but this risk increase was not substantiated in the Canadian study.[25,26]

Postnatal transmission of HSV occurs primarily from the mother or someone in the family circle with orolabial HSV. Nosocomial transmission of HSV infection by personnel has been documented in rare cases but indirect HSV transmission by inert vectors (i.e. water, contaminated object) has of yet not been demonstrated.[28] Prevention of postnatal transmission can be achieved by respecting universal precautions and direct contact restrictions of the newborn with HSV lesions.[27] Breastfeeding, which permits passive transfer of HSV antibody, is allowed by HSV infected women, except in the very rare cases where herpes lesions are present on the breast.[27]

Neonatal herpes

Compulsory notification of neonatal herpes is not mandatory in all Canadian provinces, but a 2000-2003 study conducted by the Canadian Paediatric Surveillance Program (CPSP), estimates the incidence at 5.8 cases for 100 000 births, basically the same as in Sweden, Japan and the United Kingdom, but inferior to that of the United States at 20 to 24 cases per 100 000 births.[22, 29] According to the CPSP (2003) study, over half of the cases of neonatal herpes were due to HSV-1.[22]

Neonatal herpes presents in three forms : skin, eye and mouth (SEM) infection (45%), central nervous system (CNS) disease (35%) and disseminated infection (20%).[11,27] Data from the 2003 CPSP study indicate that 63.8 % of newborns had skin, eye and mouth (SEM) infection, and 34.5 % had infection that disseminated to the central nervous system or other organs.[22] The median incubation period of HSV in the newborn is four days but the range can be between one to 28 days.[23] Herpes lesions are present in the form of skin, eye and mouth (SEM) infection in 80% of cases, and in about half of the cases for central nervous system (CNS) disease and disseminated infection, thus rendering early diagnosis difficult.[11, 30] The presence of unexplained symptoms in the newborn of a mother with a known or unknown history of herpes, such as respiratory distress, anorexia, lethargy, persistent jaundice, pyrexy and involved seizures should suggest the possibility of neonatal HSV infection and be investigated by a physician.[11, 27] There is no mortality with a strict form of skin, eye and mouth (SEM) infection, although 10% of newborns will suffer from neurological sequelae.[11, 27] There is 15% mortality with central nervous system (CNS) disease and 36% with disseminated infection. Survivors will suffer from severe morbidity such as visual disability, learning disabilities, convulsions or psychomotor delays.[3, 11, 22, 27]

Diagnostic tests

Clinical findings alone are often insufficient to confirm the presence of maternal genital HSV infection.[10, 11, 12, 13, 31] The recommended tests to confirm a herpes diagnostic are: viral identification, mainly viral culture and nucleic acid amplification as well as non-type-specific and type-specific serologic tests (Table 1).[13, 31] Because of their low sensitivity in detecting the presence of the virus itself, Tzanck cytodiagnosis and antigen searches using an ELISA method or immuno-fluorescence are not recommended.[13, 31, 32, 37] Numerous studies indicate that the nucleic acid amplification test is always much more sensitive than a culture test and can detect HSV not only from lesions at different stages but also from mucosa during asymptomatic viral shedding.[33, 34, 35] The unavailability, absence of standardization and high cost of this technique presently prevent its wide-spread use.[31]

The specimen for viral culture must be taken from the fluid contained in the vesicular lesion, the pustule or ulcer.[31] Lesions that have scabbed and dried ulcers contain very little of the virus. The swab must immediately be put in viral transport media and brought quickly to the laboratory (two to four hours).[31, 33, 34, 35] With a negative culture, a genital herpes diagnosis remains possible and use of serology tests can exclude the possibility of HSV infection. Over half of those who have just been diagnosed will stop having sexual relations and over a third will suffer from depression in the two years following the diagnosis.[10, 37] During the diagnosis of genital herpes with a pregnant woman, the midwife

Table 1: *Advantages and disadvantages of diagnosis methods*

Method	Sensitivity	Advantages	Disadvantages
Viral culture	70% from ulcers [32] 94% from vesicles [32]	Confirms the clinical diagnosis of HSV[13, 33, 34,35] Permits identification of HSV type and site of infection [13, 33, 34, 35] Relatively rapid technique (2 to 5 days) [33, 34, 35]	Viral shedding necessary for specimen collection [13, 32] Quality of specimen affected by delays, transport conditions and lesion stage [13, 33, 34,35]
NAAT Nucleic acid amplification tests	> 99 % more sensitive than HSV culture reference test[13, 33, 34,35]	Confirms the clinical diagnosis of HSV Permits identification of HSV type[13, 33, 34,35] Detects asymptomatic viral shedding [33, 34,35] Rapid technique that is little affected by transport conditions [33, 34, 35]	Can associate non-herpes lesions to HSV [33, 34, 35] Absence of standardization [13, 34,35] High cost [13, 33, 34,35] Available in only a few research laboratories [13,33 ,34, 35] No commercial kits [13, 33, 34,35]
Non-type-specific serology test	Adequate[34]	Seronegativity, 12 weeks after the appearance of lesions exclude HSV infection [13, 34, 36] Seroconversion between early and late sera, 12 weeks after the appearance of lesions, confirm a primary infection [13, 31, 34] IgM disappear in the months following a primary infection and are an indirect indication of a recent primary infection [13,34,35]	Seroconversion 3 to 6 weeks following the first contact with HSV [13] Does not permit identification of HSV type or site of infection [33, 34, 35] IgG and IgM antibody appear inconsistently during recurrent infection [13] Expensive and available in only a few laboratories [13, 31]
Type -specific serology test	96-99%[33,34,35]	Permits identification of HSV type[13] Seroconversion between early and late sera, 12 weeks after the appearance of lesions, confirm a primary infection [13, 34,36] Identifies asymptomatic carriers [13, 34] HSV-2 Seropositivity can confirm a genital HSV-2 infection[13,34]	Seroconversion 3 to 6 weeks following the first contact with HSV [13] HSV-1 seropositivity cannot identify the site of the infection, asymptomatic orolabial infections being common Expensive and available in only a few laboratories [13, 31]

must offer sensitive, empathetic and knowledgeable counselling in order to direct the woman towards necessary psychological resources. She must also convey the information to the physician who will continue the follow-up after delivery in order to offer treatment adapted to the woman's needs as well as to the severity and frequency of recurrences.[13] Furthermore, guided by the provincial regulations in effect where she practices, the midwife shall initiate a consultation or a transfer of clinical responsibility to a physician: in the case of HSV seroconversion during pregnancy (Quebec), in the presence of recurrent or primary genital herpes (Manitoba), initiate a consultation with a physician for STIs during pregnancy (Alberta, British-Columbia).[39, 40, 41, 42, 43]

Prevention, screening and therapeutic means

Table 2 presents a summary of means of screening, prevention and diagnosis of maternal genital HSV infection, recommended by the Centres for Disease Control and Prevention (2002), the International Herpes Management Forum (2002), the American College of Obstetricians & Gynaecologists (1999, 2004), the European Guidelines (2001), the College of Midwives of British Columbia (2002) and the Public Health Agency of Canada (2006).[36, 44, 45, 46,47, 48]

Prenatal screening of genital herpes relies essentially on the questioning of the pregnant woman and her partner in regard to their history of genital herpes or lesions suggestive of genital herpes. When in the presence of a history of maternal genital herpes, the College of Midwives of Manitoba's regulations recommend initiating a consultation with another midwife.[40] Over 75 % of women who are seropositive for HSV-2 do not know that they are infected.[7, 12, 49] Precise information on the possible symptomatology of genital herpes enables over half of the infected subjects who are ignorant of their diagnosis to identify symptomatic episodes of genital herpes.[27]

Compliance with prevention advice, the frequency of recurrences and sexual relations, the practice of orogenital relations, ignorance of asymptomatic

Table 2: *Summary of means of screening, prevention and diagnosis of maternal genital HSV infections*

Category	Recommendations
Pregnant women in general	Prenatal questioning regarding history of genital herpes either with the woman or with her sexual partner(s) [36,44,46,47] Contact the midwife or the physician if there are clinical signs of genital herpes either with the woman or her partner during pregnancy [13,44] Look for clinical signs of genital herpes during gynaecological exam at the onset of labour [44, 47]
Pregnant women whose partner(s) have a history of genital herpes	Offer a type-specific serology test to the woman if partner(s) have a history of HSV or if the genital herpes diagnosis was based solely on clinical observations [13,46,47] Recommend that the partner with a HSV history consult a physician to evaluate their serological status in order to offer prevention advice that is oriented to the couples needs [36, 44,46]
Seroconcordant couple	No specific prevention advice regarding sexual activities [36, 46] Encourage partner notification with a new sexual partner [13, 36, 44, 46,47] Include maternal history of HSV infections in medical record [44]
Serodiscordant couple	Systematic use of condom or dental dam during sexual activity [13, 44, 46, 47,48] Abstain from sexual activity when in the presence of prodromal symptoms or genital HSV lesions [13, 44, 47,48] Avoid direct orogenital and/or genital contact particularly during the third trimester of pregnancy for seronegative women (HSV-1, HSV-2) in order to avoid a primary maternal genital HSV infection [44, 46,47,48] Refer the infected partner to their physician for informed choice regarding antiviral therapy to reduce risk of transmission [13, 36, 44,48]
First recognized episode of maternal genital herpes	Collect culture specimen and a type-specific serology test in order to confirm the site of HSV infection and to determine the stage of the infection (primary or recurrent) [13, 36, 44,47, 48] Discuss clinical manifestations of genital herpes, asymptomatic viral shedding, modes of transmission, risk of transmission to the newborn according to type of infection, sexual risk behaviours and possible source [13,36,44,47,48] Encourage partner notification [13, 36, 44, 46,47] Offer screening tests for other STIs [13, 44] Offer psychological support and refer to a specialist for counselling on treatment options [13, 44,47] Inform the midwife or physician of clinical recurrence during pregnancy [44, 47,48]
Recurrent maternal genital herpes during prenatal period	Informed choice concerning continuous antiviral therapy, prescribed by a physician, starting at the 36th week of pregnancy [13, 36,44, 47, 48]

Web links:
http://www.herpesweb.net
The International Herpes Management Forum: http://www.ihmf.org

virus shedding as well as the use of condoms only during genital herpes episodes influence the risk of transmission.[50, 26] Systematic condom use reduces by half the risk of transmission from infected men to women, its effectiveness is reduced when HSV infected sites are not covered.[50] Daily suppressive antiviral therapy reduces almost entirely (>90%) asymptomatic viral shedding, and reduces by half the risk of transmission to the partner.[51,52]

Therapeutic and preventive effectiveness of liquorice pomade, homeopathic natrum mur, lysine, vitamin C and foods rich in argine have not been the subject of scientific studies.[48]

For pregnant women who are at risk of a recurrent infection at the time of delivery, Acyclovir (class B) continuous per os suppressive therapy, prescribed by a doctor, from the 36th week of pregnancy, reduces asymptomatic viral shedding by over 90% and reduces the presence of lesions at the time of delivery.[48, 53, 54, 55, 5 6, 57] It reduces the number of caesarean sections performed because of HSV genital lesions at the time of delivery and can avoid the transfer of clinical responsibility of the pregnant woman to a physician at the time of delivery as stipulated by the regulations of the College of Midwives of Ontario and of British Columbia as well as the Order of Quebec Midwives.[43, 48, 54] The regulations of the College of Midwives of Manitoba and of Alberta do not indicate a transfer of care but rather to initiate a consultation with a physician.[40, 42]

The need for a caesarean section, when faced with a recurrent HSV infection, before the onset of labour and the rupture of membranes can theoretically prevent fœtal exposure to HSV present in the birth canal. However, as reported in the CPSP study (2003), 24.1 % of HSV infected newborns were delivered by caesarean section.[22] According to the Randolph (1993) study, with the systematic use of caesarean section, 1,530 caesarean sections need to be performed in order to prevent one case of neonatal herpes.[58] Financial costs and maternal mortality (0.57 maternal deaths/case of

prevented neonatal herpes) would be superior to the costs associated with the prevented neonatal morbidity.[58]

Presently, only the International Herpes Management Forum (2002) Guidelines and the European Guidelines (2001) indicate that vaginal birth combined with an antiviral therapy would be acceptable during a recurrent infection with lesions at the time of delivery and should be the subject of an informed maternal choice. [45, 47] Additional studies are necessary, in order to understand the role of caesarean section in the prevention of neonatal herpes when there is a recurrent infection and the potential use of nucleic acid amplification tests to detect asymptomatic virus shedding at the time of delivery.

Conclusion

A better understanding of modes of transmission and of clinical manifestations of genital HSV infection will enable midwives to screen women at risk or infected with genital herpes, to diagnose unrecognized cases and to offer appropriate prevention advice. Offered in an informed choice manner, the means of preventing HSV genital infection must be adapted to the serological statuses of the partners and be accompanied by information on the modes of transmission of genital herpes including orogenital practices. The midwife must reassure the woman with a history of genital herpes on the low risk of transmission to the newborn. Optimal management of the pregnant woman with genital HSV infection will reduce the number of primary and recurrent genital infections during the third trimester of pregnancy and consequently the number of cases of neonatal herpes.

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