

# Herpes Simplex Virus Infection in Pregnancy

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DIAGNOSIS AND EFFECTIVE MANAGEMENT OF PRIMARY GENITAL HERPES IN THE PREGNANT WOMAN IS PARAMOUNT TO MINIMIZE THE RISK OF VERTICAL TRANSMISSION OF HERPES SIMPLEX VIRUS (HSV) TO THE FETUS OR THE NEONATE. FOR WOMEN WITH RECURRENT GENITAL HERPES DIAGNOSED BEFORE PREGNANCY, THE RISK OF TRANSMITTING HSV TO THE NEONATE IS MUCH LOWER

## KEY WORDS

■ HERPES SIMPLEX VIRUS INFECTION ■ PREGNANCY  
■ VERTICAL TRANSMISSION ■ PERINATAL HERPES INFECTION  
■ NEONATAL HERPES INFECTION ■ MANAGEMENT

## SUMMARY

The incidence of herpes simplex virus (HSV) infection has been climbing steadily in recent decades, and concerns about perinatal HSV infection are growing among women of reproductive age because of the risk of transmission of the virus to their babies during pregnancy, with potentially devastating consequences to the fetus. Neonatal infection with HSV most often occurs during labour when the baby comes into direct contact with infected maternal secretions in the birth canal. Infection can also occur while the fetus is still *in utero* or after birth, however. The risk of vertical transmission of HSV infection can be as high as 50% in women who develop a primary infection during the third trimester. There is increasing anecdotal evidence in support of the use of aciclovir in infected pregnant patients at risk of an HSV reactivation at the time of delivery, as a strategy to reduce transmission of virus from the mother to the neonate. This approach is associated with a decrease in the number of Caesarean sections required for the prevention of transmission. Trials to evaluate further the safety and efficacy of suppressive valaciclovir and famciclovir would be useful.

## Introduction

IN RECENT DECADES the prevalence of herpes simplex infection and disease has been rising. It is estimated that there are more than 500 000 new cases diagnosed each year in the USA and that more than 30 million people are infected. In Spain, the prevalence of HSV-2 antibodies was found to be 5% among a cohort of adolescents.<sup>1</sup> In contrast, the presence of HSV-2 antibodies was found to be 81% among sexually transmitted disease (STD) clinic attendees in Peru,<sup>2</sup> 32.3% among STD clinic attendees in The Netherlands,<sup>3</sup> and 27% among homosexual STD clinic attendees in London, UK.<sup>4</sup>

In most countries, herpes simplex virus type 2 (HSV-2) is the most common cause of genital herpes.<sup>5</sup> Between 20 and 30% of infected women are infected with HSV-2,<sup>6</sup> the virus type responsible for approximately 85% of cases of genital herpes infections. In some areas such as Japan, however, HSV-1 is the strain more frequently associated with genital herpes. Because of the risk of transmission of this infection to the fetus and neonate, perinatal herpes infection is of increasing concern among women of reproductive age.

## Diagnosis of Genital HSV Infections: General Considerations

The diagnosis of genital herpes is frequently missed because of a low index of clinical suspicion and the limitations of the various tests available. Available serological assays for HSV do not reliably differentiate between serotypes 1 and 2. The most accurate methods of serological testing are Western immunoblot assay (using whole virus) and immunodot assay (an enzyme-linked immunosorbent assay for type-specific glycoprotein G). These assays are sensitive and specific but are not yet clinically available.<sup>7</sup>

Viral culture is the current gold standard for the diagnosis of HSV infections but its sensitivity is limited by the duration of viral shedding, which is generally several days shorter than the duration of the lesion itself.<sup>8-10</sup> There are certain situations, however, in which recovery of viable virus may be more likely, e.g. when a first-episode lesion is present in the vesicular stage and if the lesion is sampled within 72 h of its appearance:<sup>11</sup> in such cases, culture is positive approximately 80% of the time. The likelihood of a positive result is as low as 40% if the lesion is recurrent. Aciclovir therapy further decreases the viral recovery rate.<sup>12</sup> A negative culture result does not rule out HSV infection, and cultures of serial lesions may be necessary before the final diagnosis is reached.

It is possible that DNA polymerase chain reaction (PCR) may replace viral culture as the gold standard for HSV diagnosis. DNA PCR is also more sensitive for detecting asymptomatic shedding of HSV<sup>13</sup> and, in the presence of lesions, can successfully detect viral DNA in a shorter period of time than culture.<sup>14</sup> It is unclear, however, whether detection of viral DNA corresponds to infectivity.

## Characteristics of Genital HSV Infection in Pregnancy

### RECURRENCE RATES

The recurrence rate of genital herpes appears to be higher in pregnant than in non-pregnant women, with the likelihood of recurrence increasing as the patient reaches term.<sup>15</sup> Twenty-five per cent of women with a history of genital herpes have an outbreak at some point during the last month of pregnancy, and 11-14% have an outbreak at the time of delivery.<sup>16,17</sup> Primary infection is associated with a 36% risk of outbreak at delivery.<sup>18,19</sup> A patient in whom genital herpes is diagnosed before pregnancy and who has fewer than six outbreaks per

year has a 13% risk of recurrence at delivery, whereas a woman who has six or more outbreaks per year has a 25% risk of recurrence at the time of delivery.<sup>20</sup> The incidence of asymptomatic viral shedding during pregnancy does not appear to be different from that in the non-pregnant patient.<sup>21</sup>

#### INCREASED SUSCEPTIBILITY TO SEVERE INFECTION

Natural-killer-cell cytotoxicity is attenuated during pregnancy. This physiological alteration may help support the fetoplacental allograft but it may also be associated with an increased susceptibility to various pathogens such as HSV.<sup>22,23</sup> Primary HSV infections may be more severe than in the non-pregnant patient, resulting in herpetic meningitis, hepatitis or dissemination in some cases.<sup>24,25</sup> In addition, primary infection during the second and third trimester can be associated with pre-term labour, fetal growth restriction, transplacental transmission to the fetus and spontaneous abortion.<sup>26–31</sup> Because herpes embryopathy is a very rare outcome, however, infection during the first trimester is not an indication for termination of pregnancy.<sup>32</sup>

#### HIV AND HSV SHEDDING/REACTIVATION RATES IN PREGNANCY

The prevalence of HSV-2 shedding in women who are co-infected with HSV-2 and the human immunodeficiency virus (HIV) has been shown to be nearly four times that in HIV-negative female patients.<sup>33</sup> In another study, daily cervical cultures taken during the third trimester in a small cohort of pregnant HIV-positive women (CD4<sup>+</sup> cell count: 250–300 cells/mm<sup>3</sup>) demonstrated an HSV-2 shedding rate of 12.1%. In contrast, a group of pregnant HIV-negative women with the same demographic characteristics had HSV-2 shedding rates of only 1.7%.

The data also suggest that HIV may be a co-factor in HSV reactivation during pregnancy. Among 60 deliveries in co-infected women, 8% were associated with HSV reactivation. In contrast, the overall rate of HSV reactivation in over 8000 deliveries at the same centre was 2%.<sup>34</sup>

### Vertical Transmission of HSV Infection

The potential for vertical transmission of HSV from the mother to the fetus or neonate is the source of much of the concern surrounding genital herpes during pregnancy. The risk to the infant varies with the type of maternal infection and the route of delivery.<sup>22</sup>

Transmission of HSV occurs after close contact with infected secretions. Viral shedding can occur at any time during the course of an HSV infection,<sup>35</sup> and it is widely recognized that transmission may occur while a lesion is present, whether it is a first episode or a recurrent outbreak. Viral excretion may also occur during the prodrome stage, however, at which point the patient often experiences symptoms such as tingling, itching, burning, or pain.<sup>36</sup> It is less commonly appreciated by patients that viral shedding also occurs in the absence of any identifiable lesions or prodromal symptoms.<sup>37</sup>

Infection of the neonate with HSV most often occurs during labour (90% of cases) when the baby comes into direct contact with infected maternal secretions in the birth canal.<sup>35</sup> The site of entry for the virus is usually the eye or the nasopharynx. Infection can also occur while the baby is still *in utero*, due either to an ascending infection from the cervix or vulva or as a consequence of transplacental transmission.<sup>32</sup> *In utero* infection represents 5–8% of cases of neonatal herpes infection.<sup>38,39</sup> Infection by both routes is more likely to occur during primary infections than during reactivation episodes due to the higher local and systemic viraemic loads that accompany the initial outbreak. The use of fetal scalp electrodes may also increase the risk of neonatal infection.

Many cases of neonatal infection occur after birth, when the infant is exposed to caregivers with orolabial herpes, herpetic whitlow, or lesions in other sites.<sup>40–42</sup>

Unfortunately, as with any HSV infection, transmission of the virus to the neonate at birth can also occur during periods of asymptomatic shedding. The frequency of virus isolation in the absence of lesions when tests such as PCR are used can be as high as 28% of days.<sup>43</sup> Educating patients about the possible presence of HSV in genital secretions between clinical recurrences is of great importance in helping patients to understand the risk of transmission of the infection to their partners or babies.

A series of retrospective and prospective studies suggest that the risk of transmission of genital herpes during vaginal delivery is high in neonates exposed to asymptomatic shedding or lesions (33% and 50%, respectively) in women with a first episode of genital herpes.<sup>44–46</sup> In contrast, the risk is low (3%) in neonates exposed to asymptomatic shedding or lesions in women with a history of genital herpes or who have type-specific antibodies directed against the virus isolated in culture from their genital lesions.<sup>44–46</sup> The higher risk of genital herpes in women with first episodes can be explained both by a higher virus titre and the absence of neutralizing antibodies in cord blood.<sup>44</sup> In addition, the time that it takes to develop a protective antibody response may explain the higher risk of neonatal herpes associated with a genital herpes simplex primary infection near the time of delivery.<sup>47</sup> In the absence of identifiable lesions or symptoms, the risk of HSV transmission to the neonate from a mother with a known history of genital herpes is very low (0.04%).

An important 'at risk' group is that of HSV-2 seronegative pregnant patients whose male partners are HSV-2 infected. Identification of HSV-2 serodiscordant couples in whom the woman is at risk of developing a primary infection during pregnancy is a valuable intervention that can prevent serious consequences. It is also important that pregnant women with a history of HSV-2 infection are advised to seek medical attention if they develop a lesion consistent with a herpes outbreak near the date of delivery. Culture of such lesions is likely to confirm the diagnosis, enabling informed decisions to be made about the choice of therapy and the mode of delivery.

Delivery by Caesarean section appears to decrease the risk of neonatal acquisition of HSV and has been recommended as the delivery route of choice in the presence of an active lesion.<sup>48</sup> The degree to which delivery by Caesarean section successfully prevents neonatal herpes is unknown, however, and it has been reported that 20–30% of infants diagnosed with herpes infections in the neonatal period have been delivered by Caesarean section.<sup>49</sup> In managing the pregnant woman with genital herpes, the risk of transmission should be balanced with the risks to the mother of Caesarean section.

### Neonatal Herpes

#### NEONATAL INFECTION RATES

The patterns of HSV-1 and HSV-2 seroprevalence in the maternal population may account for some of the differences in neonatal infection rates observed worldwide. Neonatal herpes can result from infection with either HSV-1 or HSV-2, and characterizes one of the most life threatening of all infections in neonates, the consequences of which are often fatal or debilitating.

In the UK, neonatal herpes is rare, the estimated incidence being 1.65/100 000 livebirths.<sup>50</sup> Reported rates are considerably higher in the USA, with 20–50/100 000 livebirths.<sup>51</sup> Comparative rates for Sweden are approximately 6.5/100 000.<sup>52</sup> The greater tendency for primary genital infection to be due to HSV-1 in the UK is likely to influence the type of neonatal infection and, therefore, may explain why similar proportions of

HSV-1 and HSV-2 neonatal infections have been found in the UK. This is in contrast to the USA, where the majority of neonatal HSV infections are HSV-2,<sup>53</sup> and primary HSV-1 infections in women are responsible for only 10% or fewer.<sup>54</sup>

#### CLINICAL MANIFESTATIONS OF NEONATAL HERPES

Neonatal herpes presents in one of three ways:

- Disease localized to the skin, eye and mouth (SEM) (Figure 1)
- Disseminated infection (involving multiple organs such as the liver, lung, adrenal glands or brain), with or without SEM involvement
- Central nervous system (CNS) disease (Figure 2), with or without SEM involvement.

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Figure 1:  
*Extensive herpetic lesions in a neonate.*

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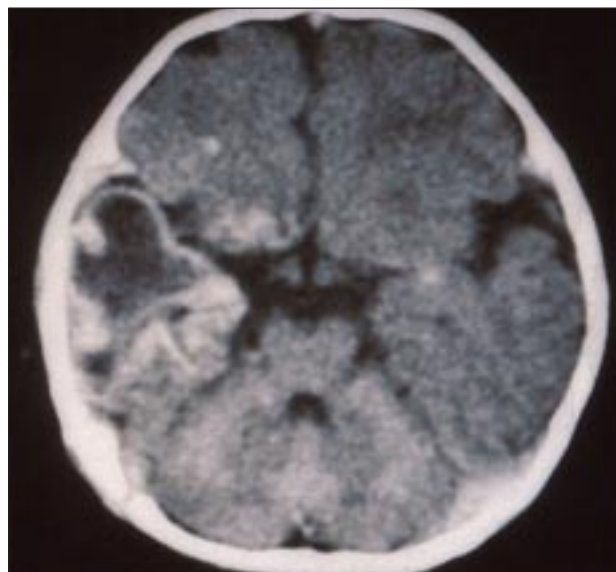


Figure 2:  
*Computed tomography scan of an infant with CNS manifestations of neonatal herpes.*

The incidence, morbidity and mortality rates for each manifestation of neonatal herpes differ considerably (Table 1). SEM is rarely fatal, whereas many neonates with encephalitis or disseminated infection die.

**SEM disease:** Neonatal herpes affecting the skin, eyes and mucous membranes occurs in 45% of cases and has the best prognosis. Typical vesicular lesions usually appear within 11 days after birth. With treatment, survival approaches 100%, and severe sequelae develop in only 5%. Approximately 2% of these cases progress to CNS disease or disseminated infection.

**CNS disease:** Central nervous system disease occurs in 35% of HSV-infected infants. Seizure activity is the presenting symptom in half of affected neonates. If patients are treated, the survival rate is much higher than in disseminated infection, approaching 85%. Sixty-five per cent of these patients suffer from serious neurological sequelae, however, such as microcephaly, hydrocephaly, porencephalic cysts, psychomotor retardation and blindness.<sup>55</sup>

**Disseminated HSV infection:** This occurs in 22% of infected neonates and is the most lethal of the three forms.<sup>56,57</sup> The initial symptoms are often non-specific, but rapid deterioration (within 24 to 72 hours) then develops.<sup>58-60</sup> Multi-organ system involvement becomes apparent, the liver and adrenal glands being particularly seriously affected. Even if the patients are treated, mortality is as high as 50%. In spite of a favourable response to therapy, neurological sequelae are present in 41% of survivors.

#### THE NEED FOR VIGILANCE IN DIAGNOSIS OF NEONATAL HERPES

Not infrequently, neonatal herpes infection is misdiagnosed because of the lack of characteristic lesions in the infant, as well as the lack of history of maternal infection. Even in the absence of a positive maternal history and vesicular lesions, neonatal herpes infections should be at the top of the differential diagnosis list whenever a neonate under 2 months of age presents with non-specific symptoms or neurological findings.

#### Management of Genital Herpes in Pregnancy

##### MODE OF DELIVERY

In 1988, the American College of Obstetricians and Gynaecologists recommended that the practice of obtaining serial HSV cultures during the last few weeks of pregnancy be discontinued, and that patients be examined when they present in labour.<sup>61-63</sup> If the patient has an identifiable lesion or she describes prodromal symptoms upon presentation, her child should be delivered by Caesarean section, regardless of how long her membranes have been ruptured. This method is somewhat controversial, as Caesarean sections do not prevent all cases of neonatal herpes,<sup>41,64</sup> but it is also important to remember that 90% of neonatal herpes infections occur at the time of birth, when the baby comes into contact with infected maternal secretions. If there are no visible lesions and no prodromal symptoms, a vaginal delivery is to be performed.<sup>64</sup> Other organizations (e.g. Centers for Disease Control) have echoed these recommendations.

##### ANTIVIRAL USE IN PREGNANT WOMEN

Worldwide, three oral antiviral therapies are available for the treatment of genital HSV infections: aciclovir, valaciclovir, and famciclovir. It is important to note that none of the antiviral drugs on the market are yet licensed for use in pregnancy. There is substantial anecdotal experience with aciclovir, however. A large registry of aciclovir use in pregnancy for both HSV and varicella pneumonia was established in the USA (1984-1998). Up until its closure in 1998, no evidence of any increase in adverse fetal effects related to drug exposure in any trimester, in comparison with the general population, was reported.<sup>65</sup>

**Table 1: Presentation and outcome in untreated neonatal herpes**

Category	%	Mortality	Morbidity
SEM	45	Uncommon	30% neurologically impaired
Encephalitis	33	75%	49–67% neurologically impaired
Disseminated	22	90%	95% neurologically impaired

**Antiviral therapy for primary HSV infections in pregnancy:** Aciclovir 400 mg three times daily has been shown to help reduce the need for Caesarean section in women whose first clinical episode of genital HSV occurred during pregnancy, without being harmful to the fetus.<sup>66</sup>

**Antiviral therapy for recurrent HSV infections in pregnancy:** Women with recognized recurrent genital herpes can be reassured that their risk of transmitting the infection is low. Suppressive aciclovir therapy has been shown to decrease the recurrence frequency in infected adults with six or more HSV reactivations per year.<sup>67</sup> This therapy has been proposed for use in pregnant women to reduce the risk of recurrence at the time of delivery and thereby decrease the need for Caesarean sections in such women.<sup>68</sup> A recent analysis showed that suppressive therapy with aciclovir in late pregnancy is a more cost-effective approach than Caesarean delivery for all women with active lesions.<sup>69</sup>

Suppressive therapy with aciclovir from 36 weeks to delivery may be offered to women with first-episode HSV during pregnancy because they are likely to either be symptomatic or shed symptomatically at the time of giving birth. Likewise, women with frequent HSV recurrences may benefit from suppressive therapy near term.

The pharmacokinetics of aciclovir have been assessed in the full-term pregnant patient. Maternal and fetal serum levels are similar, but the drug accumulates in the amniotic fluid in concentrations approximately four times greater than those in serum. This is not associated with adverse fetal or neonatal effects. Given the increased renal clearance associated with pregnancy, it is believed that the optimal dosage in this patient population is 400 mg orally, three times daily.<sup>70</sup>

In a Phase-1 trial of maternal valaciclovir therapy, it was observed that pregnant patients treated with valaciclovir achieved higher plasma aciclovir levels than did the patients who received aciclovir.<sup>71</sup> Additional trials are needed to further evaluate the safety and efficacy of suppressive valaciclovir therapy in pregnant patients.

Studies that will provide information regarding the safety and efficacy of famciclovir are ongoing.<sup>65</sup> Famciclovir treatment holds promise because of its longer intracellular half-life, but until concerns about potential mutagenicity are resolved and more information on its efficacy for suppressive therapy become available, it should not be considered for maternal suppressive therapy.

#### ANTIVIRAL USE IN NEONATES

Empirical antiviral treatment may be warranted for neonates born to mothers with primary genital herpes disease because of the 50% likelihood of transmission; however, this proposal remains controversial. Infants with known exposure should have urine, stool, eye, throat and, possibly, CSF cultures performed before discharge. Parents should be taught to recognize and report signs of poor feeding, fever, vesicles or lethargy.

Finally, if cultures performed at birth become positive following discharge, or there are abnormal CSF findings, aciclovir therapy should be instituted. The recommended neonatal dosage of aciclovir is 30–60 mg/kg/day for 10–21 days.

#### PATIENT EDUCATION

Prevention of HSV infection during gestation is important and patient education certainly plays a critical role. Studies investigating how best to prevent transmission are ongoing. Serodiscordant couples should be counselled in depth so that every attempt is made to prevent transmission to the seronegative partner, but this is particularly important when the uninfected person is a female partner of reproductive age. For women who already have genital HSV infection but wish to become pregnant, education to allow prompt recognition of a recurrence is also warranted.

#### Conclusions

Even though HSV-2 infection in pregnant women is common and rarely serious, the risk of vertical transmission to the infant when the mother develops a primary infection during the third trimester is high; this risk increases the closer to the time of delivery.

The morbidity and mortality of neonatal herpes are important and associated with serious consequences, hence the concern surrounding the disease. Prevention of infection, both of mother and neonate, remains the challenge. Unfortunately, because infection in either one presents atypically in 50% of cases, rapid identification of the problem is not always possible.

The results of viral cultures during pregnancy do not predict viral shedding at the time of delivery, and such cultures are not indicated routinely. At the onset of labour, all women should be examined and questioned about the presence of symptoms of genital herpes. The babies of women without signs or symptoms of genital HSV-2 can be delivered vaginally. Caesarean sections should be reserved for women who present active lesions, but it is important to realize that this approach does not completely eliminate risk of infection in the neonate.

Current data do not indicate an increased risk of major birth defects after aciclovir therapy, and its use may decrease the need for Caesarean deliveries. Data on prenatal exposure to valaciclovir and famciclovir are limited at present.

Infants exposed to HSV-2 during birth should be monitored carefully and, although routine use of aciclovir in asymptomatic babies is not recommended, infants with evidence of neonatal herpes should be treated promptly.

Pivotal to the prevention of HSV infection are identification of patients at risk, such as seronegative pregnant females who have seropositive partners, and patient education in general. Controlled studies are now needed to evaluate safety and efficacy of valaciclovir and famciclovir in pregnant patients.

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