Review Article

Submitted: 8.9.2017
Accepted: 28.11.2017
DOI: 10.1111/ddg.13529

Conflict of interest
None.

Vertical transmission of herpes simplex virus: an update

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Summary

Herpes simplex virus (HSV)-1 and -2 infections are highly prevalent worldwide. HSV infection during pregnancy can result in neonatal herpes infection, which is characterized by lifelong infection with periods of latency and reactivation. HSV can be acquired by an infant during one of three periods: in utero (5 %), peripartum (85 %), or postnatal (10 %). Neonatal HSV is a rare but significant infection that may be associated with severe morbidity and mortality, especially if there is dissemination or central nervous system involvement. Diagnostic and therapeutic advances have led to a reduction in mortality and, to a lesser extent, improvement of neurodevelopmental outcomes, but further developments are still needed. It is essential to improve the clinician's ability to identify infants who are at increased risk of HSV infection and to prevent mother-to-child transmission. The development of novel antiviral agents with higher efficacy is a worthwhile aim for the future.

Introduction

Herpes simplex virus (HSV) is one of the most common sexually transmitted pathogens and is responsible for genital herpes infection. Both HSV-1 and HSV-2 can cause genital herpes as wells as neonatal infection via mother-to-child transmission, which can lead to serious health problems for the newborn [1]. Maternal infection with HSV before or during childbirth can cause neonatal infection through vertical transmission or close contact. Neonatal HSV infection refers to infection within 28 days of the neonatal period, including intrauterine infection (also known as innate infection), birth canal infection, and postnatal infection [2, 3]. In order to prevent and better control HSV infection of newborns, it is necessary to fully understand the prevalence, transmission mechanisms, influencing factors as well as prevention and control measures of HSV mother-to-child transmission.

Prevalence, incidence and burden of the disease

Maternal infection with HSV is very common and is associated with lifelong infection in both developed and developing countries. The prevalence varies from country to country, which is well illustrated by the fact that in Nigeria 99.4 % of pregnant women were seropositive for anti-HSV-1 and HSV-2 IgG antibodies, while in South Africa the seroprevalence of HSV-2 infection was 58.7 %. Ethiopia had the lowest rate of African countries, with 32.1 % [4–6]. Similar to Ethiopia, the overall weighted prevalence of HSV-2 was 31.4 % in Haiti, while in Korea, Kim et al. reported an HSV-2 prevalence of 17 % [7, 8]. In the United States, between 1989–2010, 53 % of pregnant women were seropositive for HSV-1, 9 % for HSV-2 and 15 % were seropositive for both [9]. A decrease in HSV-1 and HSV-2 infections was reported in Finland, where the HSV-1 positivity rate of sera decreased

from 69.5 % to 45 % over 20 years. The seroprevalence of HSV-2 decreased to a lesser extent, from 17.5 % to 11 % [10]. However, the authors found that 48 % of women of childbearing age were at risk of primary HSV infection during pregnancy. In the Netherlands, there is also a tendency towards decreasing HSV-1 and HSV-2 seroprevalence. In 1995, the positivity rate of HSV-1 sera was 47.7 %, while for HSV-2 it was 6.8 %. By 2006, seropositivity of HSV-1 had decreased to 42.7 %, while HSV-2 seropositivity was 6.0 % [11]. In Germany, according to Korr et al., from 1997–1999 to 2008–2011 HSV-1 seroprevalence decreased from 82.1 % to 78.4 % while HSV-2 seroprevalence decreased from 13.3 % to 9.6 % (Table 1) [12]. This also means that an increasing number of adolescents lack protective antibodies against HSV-1 at the beginning of their sexual life [13]. However, HSV-1 still causes primarily genital herpes. The main risk factors for genital HSV infection are having two or more sexual partners, history of other sexually transmitted disease(s), female gender, use of contraceptives, low educational level, belonging to a minority ethnic group and sexual activity at an early age [6, 14, 15].

In case of asymptomatic infection of the mother, the alarming clinical signs are missing, so that it is difficult to recognize an HSV infection in newborns; this can lead to serious health consequences. In Australia, the incidence of HSV infection in newborns was 3.27/100,000 live births. Of these, 62.7 % were caused by HSV-1 and 37.2 % by HSV-2 [16]. In the United States in 2006, the incidence of neonatal herpes was 9.6/100,000 live births [17], but among Malawian female adolescents the incidence was much higher, 71.8/100,000 live births [18]. According to Hemelaar et al., the incidence of neonatal herpes infections in the Netherlands was 4.7/100,000 births for the period 2006–2011, which was twice as high as the incidences reported in previous studies [19]. In one of the most recent studies [20], the estimated global incidence of neonatal herpes infection was 10.3/100,000 live births, with the largest number of cases in Africa, accounting for 37 % of the global number of cases. However, the exact incidence is still not clear due to the lack of data on neonatal HSV infection (Table 2).

The mortality rate of neonatal herpes is high, even after intravenous acyclovir treatment, imposing a heavy burden on both the family and society. Treating neonatal herpes is expensive, and involves the costs of hospital stay, intensive care, intravenous drug therapy, laboratory tests, and the long-term costs of disability in case of severe neurological outcomes. According to Ambroggio et al., the cost of hospitalization was up to $37,431 per infant (quartile spacing: $14,667 to $74,519) [21].

Table 1 Prevalence of HSV1 & HSV2.

Year	HSV1/HSV2	Country	% seroprevalence	Reference
–	HSV1& HSV2	Nigeria	99.4	[4–6]
–	HSV2	South Africa	58.7	[4–6]
–	HSV2	Ethiopia	32.1	[4–6]
–	HSV2	Haiti	31.4	[7, 8]
–	HSV2	Korea	17	[7, 8]
1989–2010	HSV1	US	53	[9]
1989–2010	HSV2	US	9	[9]
1989–2010	HSV1& HSV2	US	15	[9]
1995	HSV1	Netherlands	47.7	[11]
1995	HSV2	Netherlands	6.8	[11]
2006	HSV1	Netherlands	42.7	[11]
2006	HSV2	Netherlands	6	[11]
1997–1999	HSV1	Germany	82.1	[12]
2008–2011	HSV1	Germany	78.4	[12]
1997–1999	HSV2	Germany	13.3	[12]
2008–2011	HSV2	Germany	9.6	[12]

–, not available.

Table 2 Incidence of neonatal herpes.

Year	Country	Herpes simplex	Incidence (per 100,000) live births	Reference
2006	USA	Neonatal herpes	9.6	[17]
2010	Malawi	Neonatal herpes	71.8	[18]
2006–2011	Netherlands	Neonatal herpes	4.7	[19]
2010–2015	World	Neonatal herpes	10.3 Africa highest (37 %)	[20]

Clinical types of HSV infection

HSV-1 is predominantly associated with orolabial infection, but may be responsible for genital herpes as well. HSV-2 is almost exclusively sexually transmitted, causing genital herpes. However, the number of genital herpes infections triggered by HSV-1 has increased during the past years [22]. Moreover, Brown et al. reported that HSV-1 had a higher risk of mother-to-child transmission than HSV-2 [23]. Primary HSV infections in women are mainly asymptomatic, but can present as painful erythematous papules, followed by vesicles and finally erosions on the vulva, labia major and minor, vagina and cervix, lasting for approximately 8–10 days. Recurrent herpes may be asymptomatic or symptomatic.

Types of mother-to-child transmission and main risk factors for neonatal herpes infection

HSV mother-to-child transmission can take place in the uterus (*in utero* transmission), during delivery (peripartum neonatal transmission) and after birth (postnatal HSV infection) [1, 24]. 85 % of mother-to-child HSV transmissions occur during the delivery stage, when there is viral shedding from the genital tract – particularly in secretions from the vagina. During pregnancy, both hematogenous spread and vertical transmission can lead to placental or amniotic membrane involvement, resulting in intrauterine (congenital, antepartum) HSV transmission, which accounts for 5 % of genital HSV infections. HSV can also be transmitted postnatally to the newborn, comprising 10 % of cases. Postpartum infections occur via direct contact of the newborn with HSV-infected persons, mainly from the mother by kissing, usually from her orolabial or cutaneous lesions. However, 70 % of mothers with HSV-infected newborns have no history, symptoms or signs of HSV infection at delivery [25]. A possible explanation is that recurrent genital herpes during pregnancy is more common than primary genital herpes, and recurrent genital herpes is often asymptomatic. According to Straface et al., nearly half of HSV infections in newborns were caused by the mother's recurrent genital herpes infection [26].

During pregnancy, the risk of transmission of primary genital herpes is higher than that of recurrent genital herpes. 30 % to 50 % of newborns are infected with HSV if the mother has a primary HSV infection in the third trimester [27]. In this case, there is not enough time for complete seroconversion to IgG before delivery and the infant is born without any protective passive IgG from the mother. The risk of neonatal infection is therefore highest at the time of the delivery. If a pregnant woman has primary HSV infection in the first trimester, her transmission efficiency is low; even if herpetic lesions can be observed in the genital area, the risk of neonatal infection is less than 1 % [2]. These data were confirmed by Brown et al., who found that of 177 HSV-positive and antibody-tested pregnancies, 26 pregnant women had primary genital herpes, and 151 had recurrent genital herpes at the time of delivery [28]. The results showed that the risk of neonatal herpes infection was 59.3 times as high for primary genital herpes than for recurrent genital herpes. Further analysis revealed that HSV transmission to newborns was due to primary genital herpes in 44.4 % of the cases, and by recurrent infections in 23.5 % of cases. The transmission rate of recurrent genital herpes from mother to child was only 1.3 %. Maternal HSV antibodies delivered to the fetus via the placenta have a protective effect. One major risk factor for HSV transmission from mother to child is the absence of maternal serum HSV antibody. The rupture time of the membrane is also closely related to transmission risk. Finger-Jardim et al. reported that if the time between rupture of membranes and delivery is more than six hours, the risk of retrograde infection from the cervix is approximately fourfold [29]. For mothers with active herpes at the time of delivery, the risk of neonatal HSV infection can be significantly reduced if cesarean section is performed within four hours after rupture. If the rupture time is more than four hours, regardless of the mode of delivery, almost all newborns will be infected with HSV. In case of genital herpes symptoms during pregnancy, obstetricians would probably recommend cesarean section as the preferred mode of delivery. Studies that have sought to determine whether cesarean section can

really reduce the risk of neonatal HSV infection are limited, and most have not been properly conducted. According to some studies, cesarean section can reduce the risk of mother-to-child HSV transmission [23, 30]. However, performing cesarean sections before membrane rupture cannot block the spread of HSV completely, due to the possibility of intrauterine transmission [31].

In addition to the main factors mentioned above, such as cervical HSV positivity, fetal skin integrity can also affect the efficiency of mother-to-child HSV transmission. Transmission is significantly higher if there is cervical HSV positivity. At the same time, invasive fetal monitoring and fetal examination can also increase the risk of infection [23].

Clinical manifestations of neonatal HSV infection

In case of *in utero* HSV transmission, a characteristic triad of cutaneous symptoms (vesicles, erosions, aplasia cutis, hyper- or hypopigmentation, scarring), neurological manifestations (hydranencephaly, microcephaly, intracranial calcifications, meningoencephalitis) and ophthalmologic symptoms (microphthalmia, chorioretinitis, optic atrophy) can be observed. Both primary and recurrent maternal HSV infection can lead to *in utero* transmission of the virus [32, 33].

If administration of antiretroviral treatment is not timely in cases of neonatal herpes, the mortality rate is up to 60 %. Even cases of early use of acyclovir treatment may still result in serious disability [2].

According to clinical manifestations, neonatal HSV infections acquired in the peripartum or postpartum period can be divided into three categories: the first is when the disease is confined to the skin, eyes and lips (skin, eye, and/or mouth, referred to as SEM); the second is central nervous system infection and the third is disseminated infection. The timing of the first appearance of symptoms, the characteristic findings, mortality rates and neurodevelopmental outcomes are summarized in Table 3. SEM disease is the mildest and accounts for 45 % of HSV infection in newborns. The central nervous system and other organs are not affected. [34]. Without treatment, HSV can easily lead to central nervous system infection or disseminated disease. Central nervous system infection constitutes 30 % of cases and only 65 % of the newborns will have active cutaneous lesions. Cerebrospinal fluid examination will show mildly elevated white blood cells and a slight increase in protein [35, 36]. 25 % of newborns have disseminated HSV infection. The infection can involve a variety of tissues and organs (such as brain, lung, liver, adrenal gland, skin, eyes and mouth), causing viral sepsis, respiratory failure, liver failure and disseminated intravascular coagulation (DIC), but only 60 % of the infants have active cutaneous lesions [36]. Encephalitis is the most common complication, and fever is only present in a few cases [35].

Diagnosis of genital herpes infection

Both primary and recurrent herpes infections can be symptomatic (with prodromal symptoms) or asymptomatic. In case of clinical symptoms, not every patient will have typical cutaneous lesions (papules, vesicles and erosions) with local lymphadenopathy. Laboratory tests should therefore be performed if a genital herpes infection is suspected.

Table 3 Clinical manifestations of neonatal HSV infection.

	Skin, eye and mouth (SEM) symptoms	Central nervous system infection	Disseminated disease
First appearance of symptoms	**10–12 days after birth**	**16–19 days after birth**	**10–12 days after birth**
Characteristic symptoms	Conjunctivitis, vesicles	Epilepsy, lethargy, irritability, poor appetite, unstable body temperature	Viral sepsis: respiratory failure, liver failure, disseminated intravascular coagulation
Without intravenous acyclovir			
1-year mortality rate	–	50 %	85 %
Rate of normal neurodevelopment	–	33 %	50 %
Use of intravenous acyclovir 60 mg/kg/day			
1-year mortality rate	–	4 %	29 %
Rate of normal neurodevelopment	–	31 %	83 %

Laboratory examination

To detect maternal infection, swabs should be taken from the mother's cervical and vaginal secretions or skin lesions. HSV DNA detection is now considered to be the gold standard for diagnosis. HSV DNA detection with PCR assays increases HSV detection rates significantly compared with virus culture, and the conditions for sample storage and transport are less stringent. If determination of anti-viral sensitivity is needed, cell culture should also be performed. In case of primary genital herpes, HSV typing should be done as well. Viral antigen detection methods are no longer recommended [37]. Type-specific serological tests can be used for detecting and monitoring HSV infection in pregnancy [38].

To confirm neonatal infection, isolation of HSV by culture is still the gold standard diagnostic method. Swabs should be taken 12–24 hours after birth from skin lesions, conjunctiva, mouth, nasopharynx and rectum [39].

Detection of HSV DNA from neonatal blood with PCR can confirm herpes simplex virus infection. In suspected central nervous system infection, cerebrospinal fluid (CSF) specimens can be cultured, or HSV DNA can be detected in neonatal CSF. The sensitivity of HSV DNA detection in CSF is higher than the sensitivity of virus culture; it is also suitable for HSV typing. It is therefore the preferred laboratory diagnostic method in cases of central nervous system infection [38].

Neonatal serum alanine aminotransferase (ALT) detection can be used in disseminated neonatal infection. It should be checked within 24 hours of birth; if ALT is twice as high as the upper limit of the normal range, neonatal disseminated infection can be suspected [24].

Treatment of maternal and neonatal herpes infections and prognosis of neonatal herpes infection

First episode of genital herpes

Primary genital herpes can cause severe genital ulcerations and neurologic involvement; every patient with first-episode genital herpes should therefore be treated. Pregnant women should be given intravenous acyclovir if they are severely infected, but if they have positive HSV serology without a history of genital herpes, antiviral therapy is not recommended.

According to the latest treatment guidelines (2016) of the World Health Organization (WHO), the recommended regime for the first episode of genital herpes is as follows [37, 40]:

- oral acyclovir 400 mg, 3 times a day, for 10 days; or
- oral acyclovir 200 mg, 5 times a day for 10 days; or
- oral valacyclovir 500 mg twice daily for 10 days; or
- oral famciclovir 250 mg 3 times daily for 10 days.

Recurrent genital herpes

Genital herpes recurrences usually cause minor symptoms, therefore decisions about therapy should be discussed with the patient. Oral acyclovir, famciclovir and valaciclovir can reduce the duration and severity of the symptoms. Treatment should be given within 24 hours of onset or in the prodromal phase.

WHO recommends [37, 40]:

- oral acyclovir 400 mg, 3 times a day for 5 days; or
- oral acyclovir 800 mg twice daily for 5 days; or
- oral acyclovir 800 mg, 3 times a day for 2 days; or
- oral valacyclovir 500 mg twice daily for 3 days; or
- oral famciclovir 250 mg twice daily for 5 days.

Slight differences can be observed between the WHO guidelines and the latest recommendations of the US Centers for Disease Control and Prevention (CDC). The CDC recommends [37, 41]:

- oral acyclovir 400 mg, 3 times a day; or
- oral valacyclovir 500 mg twice a day; taken from 36th week of pregnancy.

For pregnant women with frequent or severe genital herpes during pregnancy, WHO recommends long-term inhibitory regimens [37, 40]:

- oral acyclovir 400 mg twice daily or
- valacyclovir 500 mg twice daily; or
- famciclovir 250 mg twice daily for at least 6–12 months.

Treatment of neonates

In highly suspected or newly diagnosed neonatal HSV infections, immediate antiviral therapy should be administered. Early and effective antiviral therapy is the most critical factor affecting prognosis.

Treatment recommendations by the CDC are acyclovir 20 mg/kg i.v. every 8 hours for 14 days for disease limited to the skin and mucous membranes, or for 21 days for disseminated or central nervous system infection [41]. After 21 days of treatment, re-analysis of the cerebrospinal fluid is needed. If HSV DNA test of the CSF is negative, treatment should come to an end – but if the test result is positive, continuous intravenous infusions should be given until the test result is negative.

Prognosis of neonates

Comparison of low-dose therapy (i.v. acyclovir 30 mg/kg/day, every 8 hours) with high-dose acyclovir treatment (i.v. acyclovir 60 mg/kg/day every 8 hours) has shown that the higher dose can significantly improve the survival rate of

neonates with HSV infection. With high-dose acyclovir treatment, Kimberlin et al. found a mortality rate at 24 months of 31 % with disseminated disease and 6 % with central nervous system infection [42]. With low-dose acyclovir, the mortality rate at 24 months was 61 % with disseminated infection and 19 % with central nervous system infection. High dose acyclovir can also reduce the incidence of severe HSV-related neurological sequelae. The probability of normal development at 12 months of age was 6.6 times higher with high-dose acyclovir than with lower doses. In the acute phase of neonatal HSV infection, oral acyclovir improves the prognosis of the disease. In central nervous system infection, intravenous acyclovir can reduce the occurrence of neurological sequelae, and the chance of normal development of the nervous system is higher. It is therefore recommended to give oral acyclovir at a dose of 300 mg three times a day for six months after completion of intravenous therapy. However, long-term use of acyclovir may cause neutropenia in infants; the blood count should therefore be closely monitored during treatment, first at two weeks and then at four weeks after initiation of acyclovir. If the neutrophil count is normal, a monthly check is sufficient [43].

Prevention: improve mother-to-child transmission strategy

Prevention of infection during pregnancy

Pregnant women who are not infected with genital herpes should avoid sexual intercourse or genital contact during the third trimester with a partner who has known or suspected genital herpes. The preventive effect of antiviral therapy is unknown. There is no evidence that antiviral therapy reduces the risk of HSV infection of pregnant women, and it is not recommended for prevention.

The WHO and US CDC guidelines do not recommend routine HSV-2 serological screening for pregnant women. Although HSV vaccination may be the best way to prevent infection, it is still in the experimental stage. In the United States, population trials have been conducted to evaluate the effect of recombinant gD2 subunit vaccines. Recent studies have found that gV2 vaccination of women who are not infected with HSV can reduce the spread of HSV-1 and the risk of HSV-1-related genital herpes infection, but has no significant preventive effect on HSV-2 [44].

Reducing the efficiency of mother-to-child transmission includes reducing the risk of *in utero*, peripartum and postnatal virus transmission. Antiviral therapy may reduce the occurrence of genital lesions at the time of delivery, reduce the need for caesarean delivery and help to prevent postpartum infection. Since 85 % of neonatal infections occur during the delivery phase, prevention should focus on avoiding exposure of newborns to genital herpes lesions and shed viruses during birth. The US CDC has suggested that all pregnant women should be asked before labor whether they have symptoms related to genital herpes (including prodromal symptoms), and should be carefully checked for herpetic skin lesions. Performing a cesarean section before rupture of the membrane is the best protection against HSV infection if genital herpetic lesions are present. If there are no genital herpes or prodromal symptoms, cesarean section is not recommended. It should be emphasized that cesarean section cannot completely block the spread of HSV, because intrauterine infection is also possible.

Antiviral therapy can effectively reduce the recurrence rate of prenatal genital herpes and the probability of inoculation during the delivery stage, and this helps to reduce the risk of mother-to-child transmission during cesarean section. However, data regarding the efficacy of antiviral therapy in reducing the incidence of neonatal infection are still lacking and further studies are needed. It is worth mentioning that in the last five years, intensive work has been carried out on the development of an HSV-2 vaccine. This should reduce HSV 2 infection and the probability of viral transmission. Such studies are currently undergoing Phase 1 and Phase 2 clinical trials [44]. 10 % of HSV infections occur after birth, and may be due to transmission from a healthcare worker or family member [35]. HSV causes labial as well as genital herpes, and herpetic vesicles can appear on the hands as well. Virus can be also transmitted to newborns by caring, kissing, and touching. It is therefore recommended that mothers with known or suspected labial or genital herpes avoid close contact with newborns.

Conclusions

HSV mother-to-child transmission is uncommon, but can cause serious harm to the newborn. Because HSV prophylactic and therapeutic vaccines are still in the research stage, prevention of maternal infection, early detection and early antiviral therapy are still the main measures for the prevention of HSV mother-to-child transmission. Prevention of maternal infection should focus on the prevention of new infections in late pregnancy. Furthermore, in cases of first-episode genital herpes or recurrent episodes of genital herpes during pregnancy, standardized antiviral treatment should be initiated and caesarean section is advisable. Mothers with herpetic lesions should avoid close contact with the newborn.

Acknowledgement

This study was funded by grants from the National Natural Science Foundation of China (NSFC 81360236), Shanghai Hospital Development Center project (SHDC12014217) and

the Shanghai Committee of Science and Technology, China (16411961500).

This publication is supported by the National Research, Development and Innovation Fund (Hungarian NRDIF) K 120206 and by the GINOP-2.3.2-15-2016-00005 project. The project is co-financed by the European Union under the European Regional Development Fund.

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