Congenital Viral Infections:

Herpes simplex Virus –

Epidemiology, Diagnosis, Prevention

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ESCV-Workshop: Regensburg, March 11 to 13 2015
Herpes simplex virus: HSV-1 and HSV-2

83% sequence homology of their protein coding regions

Serologic crossreactivity between glycoproteins → partial crossprotection

Type specific serologic assays based on antibody response to type specific epitopes on glycoprotein G

Terminology pertaining to HSV infections

Primary infection:
- HSV-1 or HSV-2 is detected without serologic evidence of prior infection to either virus

Non primary infection:
- HSV-1 is detected in an individual with HSV-2 antibodies or vice versa

Recurrent infection:
- HSV-1 or HSV-2 is detected in an individual with serologic evidence of infection to that type of HSV
HSV-1 and HSV-2

Clinical manifestations and seroprevalence:

Orolabial HSV infections: ~ 95% HSV-1
Genital HSV infections: ~ 85% to 95% HSV-2 and ~ 5% to 15% HSV-1

Seroprevalence of HSV type 1 and 2 in Thuringia, Germany, 1999-2006

HSV: herpes simplex virus.
The bars show the 95% confidence intervals for the point estimates.

A.Sauerbrei et al: Eurosurveillance 2011
Neonatal Herpes simplex virus infection: Epidemiology

HSV-infection of the neonate is an uncommon occurrence and result from exposure to HSV during delivery following maternal genital HSV infection.

<table>
<thead>
<tr>
<th>Country/Area</th>
<th>Rate (no. per 100,000 live births)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Isles</td>
<td>1.65</td>
<td>Tookey et al; Paediatr. Perinat. Epidemiol.; 1996</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1.6</td>
<td>Pascual A. et al; Clin. Microbiol. Infect.; 2011</td>
</tr>
<tr>
<td>Canada</td>
<td>5.9</td>
<td>Kropp RY. et al; Pediatrics; 2006</td>
</tr>
<tr>
<td>USA</td>
<td>5 - 33</td>
<td>Kimberlin DW; Clin. Microbiol. Rev.; 2004</td>
</tr>
<tr>
<td>USA/Washington State</td>
<td>8.4</td>
<td>Mark KE. et al; Am. J. Obstetr. Gynecol.; 2006</td>
</tr>
<tr>
<td>USA/California</td>
<td>12.2</td>
<td>Morris SR. et al; Sex. Transm. Dis.; 2008</td>
</tr>
</tbody>
</table>
Change in HSV-1 and HSV-2 seroprevalence over time

**HSV-1**

**HSV-2**

Increase in sexual transmission of HSV-1

“HSV-1 was the major cause of genital infection by herpes simplex virus in the women included in this study “


“HSV-1 is now more common than HSV-2 as a cause of oral and genital mucosal infections in young women, but there are important age and race differences“

Bernstein DI et al: Clinical Infectious Diseases, 2014

“Herpes simplex virus type 1 genital herpes in young women: current trend in northern Finland“

Rates of neonatal herpes simplex virus (HSV) disease by serotype in Australia per 100 000 births per year, 1997–2011, with trends over time for all HSV and each serotype.

Transmission of HSV to the fetus or the newborn

HSV is transmitted during 3 time periods:

**In utero:** 5%

**Intra-Peripartum:** 85%

**Postnatal:** 10%; source: mother, medical staff, relatives, Jewish circumcision ritual

Risk factors for transmission to the neonate:

• Type of maternal infection (primary > non-primary > recurrent)
• Maternal HSV antibody status
• Type of HSV (HSV-1 > HSV-2)
• Mode of delivery (vaginal > C-section)
• Duration of rupture of membranes
• Integrity of cutaneous barrier (e.g. use of fetal scalp electrodes)
Factors influencing transmission of HSV

1. Type of maternal infection:

**Primary infection:** > $10^6$ particles /0.2 ml inoculum
viral excretion for ~ 3 weeks

Proportion of plasma samples showing herpes simplex virus (HSV) viremia, relative to time after onset of initial symptoms of primary HSV infection

Recurrent infection: ~ $10^2$ to $10^3$ particles / 0.2 ml inoculum
viral excretion for 2 to 5 days

Factors influencing transmission of HSV

2. Maternal antibody status at the time of infection and delivery

High risk: primary infection or non-primary infection late in pregnancy
→ delivery in the absence of protective maternal antibodies

Effect of maternal antibody status on neonatal transmission
(According to ZA. Brown et al; JAMA 2003)

<table>
<thead>
<tr>
<th>Maternal HSV Status</th>
<th>Rate / 100 000 Live Births (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV seronegative</td>
<td>54 (19.8 – 118)</td>
</tr>
<tr>
<td>HSV-1 seropositive only</td>
<td>26 (9.3 – 56)</td>
</tr>
<tr>
<td>HSV-2 seropositive only</td>
<td>35 (4.2 – 126)</td>
</tr>
<tr>
<td>HSV-1 and HSV-2 seropositive</td>
<td>12 (0.3 – 70)</td>
</tr>
</tbody>
</table>

CI, confidence interval
Neutralizing antibody titers to HSV 1 and HSV-2 in infants with mild and severe HSV infections and in natally exposed asymptomatic infants at birth

<table>
<thead>
<tr>
<th>HSV infection</th>
<th>N cases</th>
<th>Mean NT-titer HSV-1</th>
<th>Mean NT-titer HSV-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe*</td>
<td>11</td>
<td>1:11</td>
<td>1:11</td>
</tr>
<tr>
<td>Mild □</td>
<td>5</td>
<td>1:56</td>
<td>1:65</td>
</tr>
<tr>
<td>Natally exposed asymptomatic</td>
<td>6</td>
<td>1:85</td>
<td>1:69</td>
</tr>
</tbody>
</table>

* Encephalitis / disseminated infection
□ Skin lesions only

A.S. Yeager et al; Infection and Immunity 1980
Maternal HSV antibody avidity and risk of neonatal herpes

50% of mothers with HSV antibody avidity indexes of < 40 transmitted HSV versus 12% of mothers with HSV antibody avidity indexes of > 40

(sensitivity of this threshold: 81%, specificity: 86%)

Risk of neonatal herpes following exposure at delivery

According to Brown ZA. et al; JAMA 2003

Primary genital infection: 57%

Non-primary genital infection: 25%

Recurrent genital infection: 2%

Higher efficiency of HSV-1 transmission from mother to child, both from primary and reactivated genital HSV-1 infections compared to HSV-2

Important: 60% to 80% of women with infected infants without clinical evidence of HSV at delivery and without any history of genital HSV
Clinical presentation of in-utero infection:
Triad of skin vesicles or skin scarring, eye disease (chorioretinitis or microphthalmia), and microcephaly or hydromancephaly

Case Report: Congenital disseminated HSV-1 infection in preterm twins after primary HSV-1 infection of the mother

Premature birth at 28 weeks gestation;
Laboratory findings: leukocytosis, anemia, thrombocytopenia, elevated liver enzymes; HSV-1 DNA detected in blood and skin
Mother: at 23 weeks gestation herpetic gingivostomatitis associated with myalgias, asthenia and fever over 5 days
Disease classification and Clinical presentation of intra-peripartum HSV infections

1. **Disseminated disease**: ~25% of all neonatal HSV infections
   - presents around day 10 to 12 of life
   - involves multiple organs and presents with viral sepsis
   - two thirds have concurrent encephalitis and 40% do not develop a vesicular rash

2. **Central nervous system disease**: ~30% of all infections
   - present around day 16 to 19 of life
   - clinical manifestation include focal/generalized seizures, lethargy, irritability, poor feeding, temperature instability and bulging fontanelle
   - 60% to 70% have skin lesions at some point during the illness

3. **Skin, eye and / or mouth (SEM) disease**: ~45% of all infections
   - infection confined to skin, eye or mouth
   - present around day 10 to 12 of life
   - 80% present with a vesicular rash
Clinical presentation of neonatal HSV infection

Disseminated disease

Skin, eye and/or mouth (SEM) disease
Guidance on management of asymptomatic newborns of women with active genital HSV lesions/severe HSV infection at delivery

Evaluation of newborn at 24 hrs
1. Swabs of surface*: PCR, culture
2. Blood: PCR

If swab or blood HSV positive
1. CSF cell count, chemistry and HSV PCR
2. Serum ALT level
3. Initiation of acyclovir iv.

If CSF HSV positive and/or ALT level abnormal
Treatment for disseminated/CNS disease for 21 days

If CSF HSV negative and ALT level normal
Preemptive therapy for HSV infection for 10 days

Swabs and blood HSV negative
No evidence of HSV infection
Inform family on signs and symptoms of neonatal HSV, close follow up

*conjunctivae, mouth, nasopharynx, rectum

The American Academy of Pediatrics; Pediatrics 2013
Investigation of the mother with active genital HSV lesions/ severe HSV infection at delivery

careful anamnestic investigations
determination of the status of infection:
1. swabs of lesion and cervix: HSV-1 and -2PCR, culture
2. EDTA plasma/serum: HSV-1 and -2 PCR, testing for type specific antibodies

**primary/non-primary HSV infection:**
absence of antibodies to the detected HSV type or presence of non-neutralizing antibodies and/or presence of low-avidity antibodies to the detected HSV type
risk of transmission: ~25 – ~50%

**recurrent HSV infection:**
presence of neutralizing antibodies and/or high avidity antibodies to the detected HSV type
risk of transmission: <3%
High risk for missing the diagnosis of neonatal HSV

For infants delivered from mothers with subclinical HSV infection (esp. primary and non primary infection in late pregnancy)

They are healthy in their first days of life and are discharged from hospital. Around day 10 after birth they present with unspecific or sepsis like symptoms and in about 50% of cases without any vesicular rash. !!

→ All infants younger than 4 weeks with CNS infection or sepsis syndrome:
   laboratory testing for HSV by PCR (swabs from surface and plasma/blood)
   HSV PCR of CSF should be considered for newborns with pleocytosis
Strategies for prevention of neonatal HSV infections

Reducing acquisition of HSV-1 and HSV-2 in pregnancy:

- serologic testing of pregnant women and their partners → identification of those with discordant serologic status
- counseling women to avoid unprotected sexual intercourse/oral-genital contact in late pregnancy

Prevention of transmission:

- careful examination of cervix, vagina and vulva on admission in labor
- no fetal scalp electrodes
- cesarean section prior to the rupture of membranes recommended:
  a) presence of active genital lesions or prodromal symptoms at delivery (ACOG and Society of Obstetricians and Gynaecologists of Canada)
  b) also for women who have primary infection within 6 weeks of delivery (European guidelines for the management of genital herpes; Patel R. et al; Int.J.STD AIDS 2011)
Strategies for prevention of neonatal HSV infections

Antiviral suppressive therapy:
Initiated at week 36 of gestation is associated with a decreased likelihood of genital lesions and a reduced need for cesarean section
Subclinical viral shedding is not entirely suppressed
   cases of neonatal HSV disease despite antiviral suppressive therapy of the mother
(Pinninti SG. et al; J.Pediatrics 2012)
Risk factors for HSV acquisition among at risk pregnant women: a couples study

3.5% of HSV-1 seronegative pregnant women with HSV-1 seropositive partners acquired HSV-1. Risk for HSV-1 acquisition: partner with a history of oral herpes.

20% of HSV-2 seronegative pregnant women with HSV-2 seropositive partners acquired HSV-2. Risk for HSV-2 acquisition: duration of partnership of 1 year or less

68% of women who acquired HSV from their partners during pregnancy had subclinical infections.

Of 6 women with symptomatic HSV-2 acquisition all had genital lesions. Of 4 with symptomatic HSV-1 acquisition 3 had genital lesions.

Gardella C. et al; Am.J.Obstetr. and Gynecol.; 2005
### Cases of congenital HSV-1 infection

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>GA (w)</th>
<th>BW (g)</th>
<th>Delivery mode</th>
<th>Mother's symptoms</th>
<th>Transmission</th>
<th>Presentation at birth</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strawn</td>
<td>1973</td>
<td>ca. 28</td>
<td>ca. 1800</td>
<td>Spontaneous</td>
<td>None</td>
<td>Transplacental</td>
<td>Skin lesions</td>
<td>Iododeoxyuridine</td>
<td>Died (pneumonia)</td>
</tr>
<tr>
<td>Jewett</td>
<td>1975</td>
<td>28</td>
<td>1300</td>
<td>Spontaneous</td>
<td>Encephalitis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Died</td>
</tr>
<tr>
<td>Honig</td>
<td>1982</td>
<td>28</td>
<td>960</td>
<td>Spontaneous</td>
<td>Dysuria, vaginal pain</td>
<td>Transplacental (?)</td>
<td>Skin lesions</td>
<td>topical</td>
<td>Chorioretinitis, recurrent skin lesions</td>
</tr>
<tr>
<td>Garland</td>
<td>1991</td>
<td>30</td>
<td>1044</td>
<td>C-section</td>
<td>Flu-like</td>
<td>Transplacental</td>
<td>Skin lesions</td>
<td>Acyclovir</td>
<td>Recurrent skin lesions</td>
</tr>
<tr>
<td>Marquez</td>
<td>2011</td>
<td>34+1</td>
<td>–</td>
<td>C-section</td>
<td>Bumps on genitalia</td>
<td>Skin lesions, microcephaly, porencephalic lesions</td>
<td>Acyclovir</td>
<td>Recurrent skin lesions</td>
<td></td>
</tr>
<tr>
<td>Present paper</td>
<td>2014</td>
<td>27+2</td>
<td>750</td>
<td>C-section</td>
<td>Gingivostomatitis, myalgias, asthenia, fever</td>
<td>Transplacental</td>
<td>Skin lesions</td>
<td>Acyclovir, immunoglobulins</td>
<td>Died</td>
</tr>
<tr>
<td>Present paper</td>
<td>2014</td>
<td>27+2</td>
<td>820</td>
<td>C-section</td>
<td>Gingivostomatitis, myalgias, asthenia, fever</td>
<td>Transplacental</td>
<td>Skin lesions</td>
<td>Acyclovir, immunoglobulins</td>
<td>Died</td>
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According to Mercoloni F. et al; Z. Geburtshilfe Neonatol 2014