Herpesvirus infections in pregnancy

Dr. med. Daniela Huzly
Institute of Virology
University Medical Center Freiburg, Germany
Herpes simplex virus 1+2
Risk in pregnancy and at birth

► Primary infection in pregnancy with higher risk of complications
► Intrauterine infection possible (very rare)
► Perinatal infection (very dangerous for the baby)
  ▪ Herpes genitalis during pregnancy
► Postnatal infection
Genital Herpes

- ~5% of women of childbearing age report history of genital herpes
- HSV-2 originally called herpes genitalis (HSV-1 herpes labialis)
- Changing epidemiology over the last 20 years
Changing Epidemiology of Genital Herpes

- Retrospective analysis of genital herpes isolates in USA/Vaccine studies
  - Proportion of HSV-1 in newly diagnosed genital infection increased from 31% in 1993 to 78% in 2001
  - Vaccine studies: More than twice primary HSV-1 infections compared to HSV-2 infections
  - Seroprevalence of HSV-2 decreasing
An estimate of the global prevalence and incidence of herpes simplex virus type 2 infection

Katharine J Looker, Geoffrey P Garnett, George P Schmid

Volume 86, Number 10, October 2008, 805-812

Table 5. Regional estimates of the incidence of the herpes simplex virus type 2 infection among females, in 2003

<table>
<thead>
<tr>
<th>Region</th>
<th>15–19 years</th>
<th>20–24 years</th>
<th>25–29 years</th>
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Detection of HSV (PCR/ cell culture) in women with genital/ perianal lesions (n)

Frequencies of HSV-1 and HSV-2 in genital/ perianal lesions (%)

- HSV 1: 74
- HSV 2: 26

Freiburg University
2009-2012
Symptoms of genital herpes

- **Dependent on infection status**
  - **Primary**
    - First infection with Herpes simplex 1 or 2 without preexisting antibodies
  - **Non-primary first episode**
    - First infection with HSV 2 in HSV 1 seropositive women
  - **Recurrent**
  - **Asymptomatic viral shedding**
Herpes genitalis primary infection

- Around 2/3 of patients subclinical infection
  - Symptoms in 37% of HSV-2 cases in prospective study
- Average incubation time 4 days (2-12)
Local Pain and Itching
Fever, headache, malaise
Tender Lymphadenopathy
Dysuria

Symptoms of Primary Herpes Genitalis Infection (%)
► Reduction of ulcers without therapy after 19 days
► Complications
  ▪ Meningitis
  ▪ Myelitis
Non-primary first episode

- Partial protection from HSV-1-antibodies
  - Coinfection/Superinfection possible
- Less often symptomatic
- Duration of symptoms and shedding shorter
Recurrent HSV infection

- Homologous antibody present when symptoms appear
- Most symptoms localized
- Lower viral load, shedding few days (4), symptoms shorter (9 days)
- HSV-2 recurrence 60%, HSV-1 only 14%
  - Most recurrent infections are HSV-2
  - Most primary infections are HSV-1
Asymptomatic shedding

- First 3 months after primary infection 3x more frequent than later
- 26% of days during first year after primary, 9% in later years
- Coinfection with HIV increases asymptomatic shedding
Predictors of neonatal infection

► Highest risk with primary infection or first episode non-primary acquired near time of delivery
  ▪ 40-44% Primary
  ▪ 24-31% Non-primary
  ▪ 1-3% recurrent

► If antibodies developed before labour similar risk as recurrent

► Asymptomatic shedding: risk increases with invasive fetal monitoring, preterm birth
Risk of primary/non-primary infection

► Prospective american survey:
  Seroconversion in seronegative women during pregnancy 1.3%, 34 of 94 with symptoms

► Transmission in couples with male partner having recurrent herpes: 17%
  ▪ If antibodies to HSV-1 are present: 9%
  ▪ HSV-negative: 32%
Diagnosis – Differentiation of primary/non-primary vs. recurrent infection

► Virus-Culture and typing or type-specific PCR from swab

► HSV-IgG Screening assay
  - If IgG negative and culture/PCR positive: Diagnosis of primary infection
  - If IgG and culture/PCR HSV-2 positive: typespecific serology (glycoprotein G ELISA or Westernblot)

► HSV-IgM not useful, no differentiation of primary non-primary, not type specific
Viral shedding

- If virus culture positive at labour: 5% transmission
- 0.02% if culture negative (OR346 for positive culture)
- No data on PCR, probably too sensitive!
Cell culture
Management of genital herpes in pregnancy

Scope: Reducing risk of perinatal infection

► Serologic screening not recommended
  ▪ Increasing number of HSV-1 infections
  ▪ Possibility of false positive HSV-2 results

► Although type of HSV affects risk of transmission and neonatal sequelae (Transmission HSV1>HSV2, Sequelae HSV2>HSV1), clinical management does not take HSV-type into account
Maternal monitoring

- Weekly cultures/PCR not recommended
  - No prediction of shedding during labour
- Transcervical procedures should be avoided
- Transabdominal procedures not contraindicated
Type of delivery

▷ Caesarian section is recommended in active genital infection or with history of genital herpes and prodromal symptoms (pain, burning)
  ▪ Evidence for CS: OR=0.14

▷ Some recommend CS if primary infection in the last weeks before delivery

▷ Utility of rapid PCR before delivery not clear

▷ CS does not completely rule out neonatal infection
Therapy

- Therapy should be offered to all patients with primary/non-primary episode
- Acyclovir safe at all stages, Valacyclovir seems to be safe
  - Reduction of symptoms, complications and duration of shedding
- Suppressive therapy: recurrent herpes from 36 week of gest.
  - Effect on transmission not shown
  - Cases of neonatal infection with suppressive therapy documented
Herpes neonatorum

- Defined as herpes infection in the first month of life

- Transmission
  - Intrauterine – very rare
  - Perinatal – 85%
  - Postnatal – 10% (US, other countries no actual data)
    - Caretaker or sibling with HSV lesion and neonate antibody negative
  - Incubation time dependent on route of transmission
Herpes neonatorum - Symptoms

- Up to 50% without skin lesions
- Uncharacteristic symptoms at the beginning
- Different pictures
  - SEM – localized to skin, eye and mouth: 30-45%
  - CNS infection with or without SEM: 35%
  - Disseminated disease – hepatitis, pneumonitis, encephalitis, sepsis: high mortality
- More than 20% without skin vesicles
Herpes neonatorum - diagnosis

► History of genital herpes in pregnancy and vaginal delivery: swab from mouth, eye, anus 24h post partum – PCR
► With lesions: swab from lesion
► Without lesion: Blood and cerebrospinal fluid – PCR
  ▪ Should be included in neonatal sepsis work-up
► Serology not usefull!!!!!
Case 1

- Baby develops fever, thrombopenia, hepatitis and then sepsis-like syndrome from 6th day p.p.
- History: delivery by cesarean section in 38th week of pregnancy (mother developed flu-like illness with oesophagitis)
- „TORCH“ serology „normal“
After 4 days without specific findings and despite empiric antibiotic treatment situation deteriorates and baby finally dies

Histology shows inclusion bodies in hepatocytes

PCR from liver and blood: HSV-1-DNA highly positive

HSV-IgG negative
What had happened?

- Primary infection with HSV-1 during late pregnancy, complicated by oesophagitis
- Infection possibly acquired postnatally (saliva of mother highly infective) or via blood stream with viraemia
Case 2

► One twin girl from day 7 uncharacteristic symptoms with hepato-splenomegaly, sucking weakness, hypothermia

► Beginning with antibiotic therapy, no effect, liver enzymes rising, abdominal distension

► Weekend, empirical start of Acyclovir 45mg/kg/8h („looks like viral disease“)

► Monday: virological work-up (HSV, enterovirus, parechovirus)
HSV-1-DNA in blood (from Friday) 14 mio copies/ml

Oral swab from beginning of symptoms retrospectively analyzed: HSV-1 positive

Baby gets better every day

After 3 weeks of therapy baby well and healthy
Herpes neonatorum - Therapy

► Suspect of infection (don’t wait for result): 45mg/kg/day i.v. (8h) for localized symptoms, 60mg for CNS or disseminated disease
  ▪ 14 days/21 days
► If PCR post partum positive: 14 days
► CNS: >80% sequelae
  ▪ Debate: Suppressive therapy for 3-6 months
► Mortality of disseminated disease despite therapy 56%
Mother, father and grandmother of baby2: HSV-seronegative – nosocomial infection!

65-80% of adults seropositive for HSV-1

HSV shedding in 1% of days of infected children and 5-10% of days of infected adults!
Thank you for your attention