Genital Herpes in Pregnancy

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Ob/Gyn PGY3
Perinatal Rounds
November 3, 2009
Case A – Ms. Jenny T. Al-Herpes

- 28 yo G1P0 female presented to office for prenatal care at 16 weeks GA
- Uneventful pregnancy thus far
- Past O&G hx: genital herpes since age 21, 1-2 outbreaks/year
- PMHx: none
- PSHx: none
- Meds: Acyclovir prn
- Allergies: none
- SocHx: Married. Secretary. No smoking/EtOH/drugs.
Case A – Ms. Jenny T. Al-Herpes

- Pregnancy uneventful aside from one flare-up of genital herpes at 20 weeks GA, for which she was prescribed Acyclovir 400mg po tid x 5d
- 36 weeks GA: began prophylactic Acyclovir 400mg po tid
- 39 weeks GA: presented to hospital with early labour
  - no genital herpetic lesions
  - had SVD, healthy baby
Case B – H.H.

- Married 15 yo G1P0
- 31+ weeks GA: presented to community hospital with spotting and preterm labour
- Prenatal care sporadic
- No prior or recent history of herpes
- On exam:
  - AVSS
  - VE: Membranes intact
  - U/S: Fetal ascites and possible microencephaly

Case B – H.H.

- Transfer to tertiary hospital
  - NST: 150 bpm baseline, episodes of fetal bradycardia in 60s with ctn’s
- Emergency C/S performed:
  - Female infant, amniotic fluid foul-smelling and discoloured
  - APGAR 0¹ 0⁵
  - Resuscitation by NICU unsuccessful
Case B – H.H.

- Autopsy:
  - 1200-g female infant
  - No malformations (no microphthalmia, short digits, or limb abnormalities)
  - Skin - ++ ulcerated and encrusted over R face, and over scattered areas of trunk and extremities
  - Liver - multiple irregular, soft, yellow lesions
  - Brain – asymmetric, R<L cerebral hemisphere
  - Placental membranes – cloudy

- Microscopic findings: Many organs showed signs of necrosis and inflammation

- Immunohistochemical and FISH findings: +ve HSV Ag and Ab (serotyping unavailable)

- Mother’s blood sample: +ve HSV2 IgG, -ve HSV1 IgG

Introduction

- HSV one of most common viral STIs worldwide
- HSV2 responsible for majority of genital herpes, almost always sexually transmitted
- HSV1 usually transmitted during childhood by non-sexual contacts, BUT increasingly becoming a cause of genital herpes, esp. among young adults
- HSV infection in pregnant women a concern as vertical transmission may lead to poor outcomes for baby

Epidemiology – HSV1

- Prevalence ↑s with age globally
  - 40% by age 15
  - 60-90% in older adults

Epidemiology - HSV2

- US: 23% in women, 11% in men
- Sub-Saharan Africa: 30-80% in women, 10-50% in men, > 80% of sex trade workers
- Asia: 10-30% of general pop.
- Generally women > men

- Problem: Majority of infected people are NOT diagnosed with genital herpes (no lesions, or lesions mild/unrecognized) → asymptomatic shedding → transmission

Epidemiology - HSV2

Risk factors:
- # sexual partners
- Ethnicity
- Poverty
- Cocaine abuse
- Early onset of sexual debut
- Sexual behaviour
- Bacterial vaginosis

Transmission of HSV

- Primarily by exposure to:
  - Mucous membranes
  - Active lesions on skin
  - Mucosal secretions of person with active infection (saliva, genital discharge, etc.)
  - Mucocutaneous secretions from person with asymptomatic shedding

Chayavichitsilp et al. Pediatrics in Review 2009;30;119-130
## Transmission of HSV

<table>
<thead>
<tr>
<th></th>
<th>1° infection</th>
<th>Recurrent infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incubation period</strong></td>
<td>2-12 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Virus transmitted during this period</td>
<td></td>
</tr>
<tr>
<td><strong>Active shedding period</strong></td>
<td>Long - up to 21 days</td>
<td>3-4 days</td>
</tr>
</tbody>
</table>

Chayavichitsilp et al. Pediatrics in Review 2009;30;119-130
SOGC Classification of Genital Herpes

- 1° infection: occurs when encountering HSV1 or 2 and has no prior exposure (i.e., Ab negative)
- Non- 1° first episode: first clinically recognized episode, but has Abs from prior exposure
- Recurrent infection: clinically evident recurrent episode in individual with positive Abs

Clinical Manifestations of 1° Genital Herpes

- Small vesicles on erythematous base → rupture into painful, shallow, gray erosions or ulcerations +/- crusting
- Locations: external genitalia, cervix, internal thigh, buttocks, perianal skin
- Other symptoms:
  - Burning and paresthesia at site
  - Systemic - fever, malaise, myalgia, headache, lymphadenopathy
  - Dysuria
  - Vaginal discharge
  - Autonomic neuropathy → urinary retention

Clinical Manifestations of 1° Genital Herpes

- Meningitis:
  - Common with 1° genital herpes (42% with HSV2, 12% with HSV1)
  - Rare with recurrent infection – (1% of HSV1/2)
- Severe disease (rare – case reports): hepatitis, encephalitis, disseminated HSV

Clinical Manifestations of Genital Herpes in Latent phase

- Virus dormant in sacral sensory ganglia of autonomic nervous system
- Replicates while evading detection by host immune system - incurable
- Asymptomatic virus shedding:
  - HSV can reactivate in sensory ganglion → travel via axons back to genital mucosa without clinical signs/symptoms
  - Majority of sexual HSV transmission occurs this way because pt’s unaware of shedding
  - Occurs more with HSV2 than with HSV1 infection (7% vs 2%)
  - More frequent in person with recent 1° infection, near the time of clinical recurrences (before and after), and immunocompromised

Chayavichitsilp et al. Pediatrics in Review 2009;30;119-130
Clinical Manifestations of Recurrent Genital Herpes

- Triggered by internal or external stimulus (stress, sunlight, fever, menstruation, fatigue) → virus travels along sensory nerve to same mucocutaneous region as 1° infection and is reactivated
- Presence of IgG vs. virus → outbreaks less severe
  - Shorter duration (7-10 days), lesions fewer and smaller, systemic symptoms rare
- Prodromes may occur hours – days before episode
  - Itch, tingling, neuralgia
- Most of recurrent genital herpes due to HSV2 because it reactivates more frequently than HSV1

Differential Diagnoses of Genital Herpes

- **STIs**
  - Syphilis
  - Chancroid
  - Condyloma acuminatum
  - Lymphogranuloma venereum

- **Non-STIs**
  - Candida
  - Scabies
  - Lichen planus
  - Lichen sclerosus
  - Behcet syndrome
  - Herpes zoster
  - Trauma

Guess the lesion

a) Genital herpes
b) Syphilis
c) LGV
d) Chancroid

Chayavichitsilp et al. Pediatrics in Review 2009;30;119-130
Guess the lesion

a) Lichen planus
b) Lichen sclerosus
c) Behcet syndrome
d) Genital herpes

b) Lichen sclerosus
Guess the lesion

a) Behcet’s syndrome
b) Chancroid
c) Syphilis
d) Genital herpes

c) Syphilis

www.safersex.co.za/stdsyphilis.htm
Guess the lesion

a) Lichen planus
b) Lichen sclerosus
c) Candida
d) Genital herpes

Mandell: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th ed. Accessed through MD Consult.
HSV Infection in Pregnancy

- HSV2 seropositivity in pregnant Canadian women: 7 – 28%
- Only 2% acquire 1° genital herpes during pregnancy
- Pregnant state can complicate 1° infection
  - Rarely can develop disseminated skin lesions with visceral involvement → hepatitis, encephalitis, thrombocytopenia, leukopenia, coagulopathy
  - mortality 50%

Roberts et al. Sex Trans Dis 2003;30:797-800.
Maternal-Fetal Transmission

- Neonatal incidence 1/17,000 live births in Canada
- 1° genital herpes near time of delivery → high risk of vertical transmission (30 - 50%) due to inadequate time to develop Abs to suppress infection before labour
- 1° or recurrent genital herpes during first half of pregnancy → low risk of vertical transmission (<1%)
- BUT, because recurrent genital herpes much more common than 1° infection during pregnancy, # neonatal HSV infections due to recurrent herpes significant

Maternal-Fetal Transmission

- Vertical transmission via asymptomatic viral shedding also significant because neonatal infection may be missed
- Transplacental transmission to fetus during pregnancy uncommon
- NOT transmitted through breast milk

### Classification of Congenital and Neonatal Herpes

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Timing of acquisition</th>
<th>% of neonatal HSV infections</th>
<th>Mode of acquisition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Antepartum</td>
<td>5%</td>
<td>Transplacental</td>
</tr>
<tr>
<td>Neonatal</td>
<td>Intrapartum (at or near birth)</td>
<td>85-90%</td>
<td>Genital exposure</td>
</tr>
<tr>
<td>Neonatal</td>
<td>Postpartum</td>
<td>5-10%</td>
<td>Nosocomial (staff/family direct skin contact)</td>
</tr>
</tbody>
</table>

Congenital Herpes

- 90% due to HSV2
- Risk of transplacental transmission highest during first 20 weeks GA → abortion, stillbirth, congenital anomalies
- Survivors:
  - Vesicular skin lesions
  - Eye lesions (chorioretinitis, microphthalmia, cataract),
  - Neurologic damage (microcephaly, intracranial calcifications, seizure, encephalomalacia)
- Unlike neonatal herpes, NO systemic disease
- ~ All affected infants will have developmental delay

Neonatal Herpes

- 70-85% of neonatal herpes caused by HSV2
- Infection with HSV2 associated with poorer prognosis, but severe cases have been found with HSV1 infection
- Correlated with preterm birth – up to 40% of babies with neonatal herpes premature

Clinical Features of Neonatal Herpes

1) Skin, eye, mouth (SEM) infection
   - Caused by direct contact with mother’s genital lesions
   - Rarely fatal, but 38% may develop neurological sequelae

2) CNS disease
   - Encephalitis +/- skin, eye and mouth infection
   - Symptoms - seizure, lethargy, hypotonia
   - Accounts for 60% of neonatal herpes cases
   - Mortality rate 5%
   - Permanent neurologic disorders in up to 40% of survivors

3) Disseminated disease
   - Multisystem involvement – shock, DIC, multiple organ failure
   - > 50% mortality if untreated

Neonatal Herpes


Figure - Cutaneous lesions of neonatal HSV infection.
Dx of Congenital and Neonatal Herpes

- Dx made on clinical presentation and/or + culture from neonate
- HSV culture of blood, urine, CSF
- Surface cultures from skin vesicles, conjunctiva, nasopharynx, throat, rectum
- + surface cultures >48 h after birth → indicates neonatal infection, not contamination from intrapartum exposure
- If suspected → early consultation with pediatrician or peds ID

Management of Congenital and Neonatal Herpes

- Acyclovir IV should be initiated ASAP → evidence of ↓ mortality (58% to 16%) and neurological sequelae
  - If only SEM disease: 60 mg/kg/day divided q8h x 14d
  - If CNS/disseminated disease: 60 mg/kg/day x 21d
  - Step-down to po acyclovir x 6 mo for prevention of recurrent CNS infection → Phase III trial results pending
  - Infants with ocular involvement should also receive antiviral eye drops
- Insufficient evidence for routine antiviral prophylaxis for asymptomatic infants

Diagnosis of Genital Herpes in Pregnancy

- Direct methods
- Indirect methods (serologic assay)
Diagnosis of Genital Herpes in Pregnancy

- **Viral cell culture**
  - Gold standard
  - Vigorously swab base of an unroofed (open) vesicle
  - Inoculate swab into culture medium → culture medium → watch for characteristics of HSV infected cells (multinucleated giant cells, intranuclear inclusions)
- **Viral typing possible (HSV 1 or 2)**
  - Useful to know because HSV1 causes more severe initial outbreak but fewer recurrences than HSV2
  - Not essential to know because tx same for HSV1 and 2

Diagnosis of Genital Herpes in Pregnancy

- Viral cell culture
  - Sens:
    - Vesicle: > 90%
    - Ulcer: 95%
    - Scab: 70%
    - Mucosa without lesions: 30%
  - Spec: ~100%
- Disadvantages:
  - Takes 2-7 days
  - Only in specialized labs

Diagnosis of Genital Herpes in Pregnancy

- **Direct fluorescent antibody (DFA) testing**
  - Ab tagged with fluorescence $\rightarrow$ mixed with tissue specimen from lesion $\rightarrow$ forms Ag-Ab complex with HSV Ag’s
  - Can be performed with viral cell culture specimen or cytologic preparation
  - Rapid (<4h), inexpensive, serotyping possible
  - Sens 41-80%, Spec 80%

Diagnosis of Genital Herpes in Pregnancy

- **PCR for HSV DNA**
  - Can sample skin lesions, vesicular content or mucosa without lesions
  - Sens: 97-98%
  - Spec: ~100%
  - Rapid - results within 24-48h
  - Viral typing possible

- **Disadvantages:**
  - Not FDA-approved yet for genital specimens (used for CSF analysis in suspected CNS infection with HSV)
  - Only in specialized labs

Diagnosis of Genital Herpes in Pregnancy

- **Cytology (Tzanck’s smear)**
  - Scrape cells from base of freshly opened vesicle → stain and look for characteristics of HSV infected cells
  - Rapid, inexpensive
  - Sens: 73-100%
  - Spec: ~100%
- **Disadvantages:**
  - Cannot perform viral typing
  - Sensitivity variable depending on evaluator

Diagnosis of Genital Herpes in Pregnancy

- Direct methods available at Prov Lab in Edmonton:
  - Viral cell culture
  - DFA testing
  - (PCR and Tzanck’s smear not available)
Diagnosis of Genital Herpes in Pregnancy

- **Enzyme Immunoassay (EIA)**
  - Serologic assay for detection of Ab to HSV Ag
  - Takes longer to complete than other techniques
  - Indications:
    - Differentiating between 1° and recurrent infections
    - No active lesions to swab
    - Testing partners of persons with known herpes
  - Take two samples:
    - Acute sample (within 3-4d after onset of symptoms)
    - Convalescent sample (several weeks after onset of symptoms)
      - If 1° infection → acute sample –ve, conv sample +ve for IgM and IgG
      - If recurrent infection → both samples +ve
      - If no infection → both samples –ve
  - Sens 80-98%, spec >96%

Prevention of Neonatal Herpes

- Key principles of prevention of neonatal herpes:
  - Preventing acquisition of genital herpes during late pregnancy
  - Avoiding exposure of infant to herpetic lesions during delivery

Prevention of Neonatal Herpes During Pregnancy: Antenatal Counseling

SOGC
If HSV discordant couple identified (i.e., pregnant woman sero-ve and partner sero+ve):
- Abstinence from oral-anogenital and anogenital-anogenital contact
- If this is not possible:
  - Condom use
  - Consider antiviral suppression in partner

CDC (US)
Women w/o known genital herpes:
- Avoid intercourse during T3 with partners known/suspected to have genital herpes

Women w/o known orolabial herpes:
- Avoid receptive oral sex during T3 with partners known/suspected to have orolabial herpes

Serial antenatal genital viral cultures of women with hx of genital herpes NOT predictive of neonatal herpes → should not be done

Management of 1° Genital Herpes During Pregnancy

- Tx with antivirals, including in T1, may be appropriate if maternal symptoms severe
- Perform viral culture and serial EIA to determine if infection 1° or non-1° first episode → guides counseling on mode of delivery and use of antiviral prophylaxis
- If first clinically recognized episode occurs near delivery and serostatus cannot be determined, treat as 1° infection
- 1° infection in T3:
  - Acyclovir po (iv if pt requires hospitalization)
  - Elective C/S
  - Consult ID
- Perform HSV cultures on neonate, and observe for signs of HSV infection
  - Instruct parents of signs/symptoms of HSV to watch for

Mode of Delivery

- At onset of labour:
  - Ask if pt has a hx of genital herpes
  - Screen for symptoms of genital herpes
  - Examine for herpetic lesions

- Women without signs/symptoms of genital herpes or its prodrome can deliver vaginally; if + signs/symptoms or prodrome → C/S

- In management of labour in women with hx of recurrent genital herpes, avoid scalp electrodes and fetal scalp sampling

[Link to CDC website]

Mode of Delivery

- C/S recommended even if lesions remote from vulvar area (buttocks, thighs) due to risk for concurrent cervical or vaginal shedding of virus.
- C/S should be performed w/in 4h of ROM.
- If delivery imminent, likely no benefit to C/S.
- Prolonged ROM with active genital herpes → protective effect of C/S not proven.

Antiviral Prophylaxis
Near Term

- Antiviral agents against HSV: acyclovir, valacyclovir, famciclovir
  - Nucleoside analogues → inhibits viral DNA synthesis
  - All shown to reduce symptoms and viral shedding in non-pregnant adults with genital herpes

Antiviral Prophylaxis Near Term

- Cochrane Systematic Review Jan 2008
- Criteria for inclusion:
  - RCTs that used antiviral agents (acyclovir, valacyclovir, famciclovir) starting at 36 weeks GA as prophylaxis for recurrent genital herpes at delivery
  - Participants: Pregnant women who have been dx’ed with genital herpes before or during pregnancy
  - Interventions: PO antiviral vs. placebo or no tx starting at 36 weeks GA until delivery
  → 7 RCTs (1249 participants) met criteria

Hollier et al. Cochrane Database of Systematic Reviews 2008;1. CD004946.
Antiviral Prophylaxis
Near Term

- Outcomes being studied:
  - 1°: Neonatal herpes
  - 2°:
    - Rate of recurrent genital herpes at delivery (dx’ed clinically)
    - # C/S performed for clinical HSV recurrences or prodromal symptoms
    - Prevalence of HSV detection at delivery (dx’ed by culture or PCR)

Hollier et al. Cochrane Database of Systematic Reviews 2008;1. CD004946.
Antiviral Prophylaxis
Near Term

1) Antiviral vs. placebo for neonatal herpes
   - Incidence 0/646 in antiviral group
   - Incidence 0/594 in placebo/no tx group
   → Due to low incidence, insufficient evidence to determine if antiviral prophylaxis reduces risk of neonatal herpes
Antiviral Prophylaxis
Near Term

2) Antiviral vs. placebo for genital herpes recurrence at delivery

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H(95% CI)</td>
<td></td>
<td>M-H(95% CI)</td>
</tr>
<tr>
<td>1 Acyclovir</td>
<td>20/167</td>
<td>15/121</td>
<td>19.9 %</td>
<td>0.02 [0.00, 0.39]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/31</td>
<td>6/32</td>
<td>6.6 %</td>
<td>0.34 [0.06, 1.58]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/65</td>
<td>10/29</td>
<td>10.5 %</td>
<td>0.22 [0.05, 0.93]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7/116</td>
<td>16/115</td>
<td>17.8 %</td>
<td>0.34 [0.19, 1.01]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4/84</td>
<td>11/78</td>
<td>12.7 %</td>
<td>0.34 [0.11, 1.02]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>424</td>
<td>375</td>
<td>67.5 %</td>
<td>0.25 [0.15, 0.43]</td>
<td></td>
</tr>
</tbody>
</table>

Overall (Acyclovir + Valacyclovir groups):

RR = 25/651 ÷ 87/598 = 0.28 [0.18 – 0.43]
1/0.28 = 3.6

ARR = 0.107

NNT = 9.3
### Antiviral Prophylaxis Near Term

3) Antiviral vs. placebo for C/S

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H/Rr95% CI</td>
<td></td>
<td>M-H/Rr95% CI</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>0/167</td>
<td>15/121</td>
<td>203.8%</td>
<td>0.02 [0.02, 0.39]</td>
<td></td>
</tr>
<tr>
<td>Brocklehurst</td>
<td>4/31</td>
<td>8/32</td>
<td>9.1%</td>
<td>0.52 [0.17, 1.54]</td>
<td></td>
</tr>
<tr>
<td>Scott 1996</td>
<td>0/26</td>
<td>10/29</td>
<td>11.3%</td>
<td>0.05 [0.02, 0.39]</td>
<td></td>
</tr>
<tr>
<td>Scott 2002</td>
<td>8/16</td>
<td>14/13</td>
<td>16.3%</td>
<td>0.37 [0.25, 1.30]</td>
<td></td>
</tr>
<tr>
<td>Watts 2003</td>
<td>3/84</td>
<td>8/78</td>
<td>9.6%</td>
<td>0.35 [0.10, 1.37]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>424</td>
<td>375</td>
<td>67.3%</td>
<td>0.27 [0.16, 0.46]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events 15 (Treatment)</strong>, 55 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity $\chi^2 = 8.69$, df = 4 ($P = 0.07$), $I^2 = 54%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect $Z = 4.84$ ($P &lt; 0.0001$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valacyclovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andrews 2006</td>
<td>3/57</td>
<td>7/55</td>
<td>8.2%</td>
<td>0.41 [0.11, 1.52]</td>
<td></td>
</tr>
<tr>
<td>Sheffield 2006</td>
<td>7/70</td>
<td>21/168</td>
<td>24.5%</td>
<td>0.33 [0.14, 0.75]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>227</td>
<td>223</td>
<td>32.7%</td>
<td>0.35 [0.17, 0.70]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events 10 (Treatment)</strong>, 28 (Control)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Heterogeneity $\chi^2 = 0.01$, df = 1 ($P = 0.77$), $I^2 = 0%$</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect $Z = 2.94$ ($P = 0.0033$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>651</td>
<td>598</td>
<td>100.0%</td>
<td>0.30 [0.20, 0.45]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events 25 (Treatment)</strong>, 83 (Control)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity $\chi^2 = 8.25$, df = 6 ($P = 0.22$), $I^2 = 27%$</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect $Z = 5.65$ ($P &lt; 0.0001$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Overall (Acyclovir + Valacyclovir groups):**

$RR = 0.30 [0.20 – 0.45]$

$1/0.3 = 3.3$

$ARR = 0.10$

$NNT = 10$
Antiviral Prophylaxis Near Term

4) Antiviral vs. placebo for genital HSV detection at delivery

Overall (Acyclovir + Valacyclovir groups):

RR = 0.14 [0.05 – 0.39]
1/0.14 = 7.1

ARR = 0.058

NNT = 17.2
Antiviral Prophylaxis
Near Term

5) Antiviral vs. placebo for neonatal viral detection

Risk ratio = 1.63 [0.22 – 12.13]
→ non-significant
Antiviral Prophylaxis Near Term

- Summary - antiviral prophylaxis reduces risk of:
  - Clinical recurrence of genital herpes at delivery
  - C/S for clinical recurrence of genital herpes at delivery
  - Lab detection of genital HSV at delivery

Hollier et al. Cochrane Database of Systematic Reviews 2008;1. CD004946.
Antiviral Prophylaxis – Neonatal/Maternal Harm?

- 2 RCTs on valacyclovir vs. placebo (N=350 and N=112)
- No difference in neonatal outcomes:
  - Birth weight
  - Rate of preterm birth
  - 5 min Apgar score < 7
  - Laboratory evaluations (hematologic/hepatic/renal)
  - NICU admission rate
  - Neonatal sepsis
  - Ventilator requirement
- No difference in maternal outcomes:
  - No renal toxicity
  - Valacyclovir tolerated well with only minor side effects

Antiviral Prophylaxis – Long-term Harm in Children?

- **Acyclovir-In-Pregnancy Registry (1984-1999):**
  - Prospectively followed 1129 acyclovir-exposed pregnancies (including 712 T1 cases) → no difference in rate of birth defects compared to baseline

- **Valacyclovir-In-Pregnancy Registry (1995 - 1999):**
  - Insufficient data to comment on potential teratogenicity

http://pregnancyregistry.gsk.com/acyclovir.html
Antiviral Prophylaxis – Choice of Drugs

- Acyclovir vs. Valacyclovir vs. Famciclovir (all Category B):
  - Acyclovir:
    - Longer history of use in pregnancy → more safety data
  - Valacyclovir:
    - Prodrug of acyclovir
    - Longer t1/2 → less frequent dosing → may improve compliance
    - Data available on its use in suppressive therapy after 36 weeks GA, but scant data on its use earlier in pregnancy
  - Famciclovir:
    - Concerns about teratogenicity and carcinogenesis with famcyclovir in animal studies
    - No human studies yet → not recommended for use in pregnancy

### Antiviral Prophylaxis – Dosing Regimens

<table>
<thead>
<tr>
<th>Type of genital herpes</th>
<th>Antiviral</th>
<th>Dosing</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Acyclovir</td>
<td>5mg/kg iv q8h 400mg po tid</td>
<td>Switch to po ASAP 7-10 days</td>
</tr>
<tr>
<td>Recurrent</td>
<td>Acyclovir</td>
<td>400mg po tid</td>
<td>5 days</td>
</tr>
<tr>
<td>Suppressive tx near term</td>
<td>Acyclovir</td>
<td>400mg po tid or 200mg po qid</td>
<td>From 36 wk till delivery</td>
</tr>
<tr>
<td></td>
<td>Valacyclovir</td>
<td>500mg po bid</td>
<td>From 36 wk till delivery</td>
</tr>
</tbody>
</table>

Note: Various dosing regimens available (no national/international consensus on dosing in pregnancy)


Blondel-Hill et al. Bugs & Drugs 2006
Antiviral Prophylaxis – Choice of Drugs

- **Cost:**
  - Acyclovir 400mg po tid → $13/day
  - Valacyclovir 500mg po bid → $13/day
    (generic pricing)

London Drugs Pharmacy, Edmonton, AB.
Antiviral Prophylaxis

- Note: For recurrent outbreaks during pregnancy, continuous antiviral use is not recommended prior to 36 weeks GA, BUT if manifestations very severe or unacceptable to pt, or if preterm delivery is predicted, therapy can be individualized.

Genital Herpes and PPROM

- Preterm premature rupture of membranes in woman with hx of recurrent genital herpes
  → antiviral prophylaxis recommended until delivery

On the Horizon: Vaccine Against HSV?

- Hx of many failed attempts
- Phase III RCT of HSV2 glycoprotein-D vaccine with adjuvant in women whose partners had hx of genital herpes (GlaxoSmithCline)
  - Study 1: 268 women and 579 men (18-45yo) sero-ve for HSV1 and 2
  - Study 2: 710 women and 1157 men (18yo and up) sero-ve for HSV2
- All women received either vaccine or placebo at 0, 1 and 6 mo → evaluated at 19 mo for occurrence of genital herpes

On the Horizon: Vaccine Against HSV?

- Results:
  - 73% efficacious in women who were sero-ve for both HSV1 and 2 at baseline
  - Not efficacious in women who were sero+ve for HSV1 and sero-ve for HSV2 at baseline
  - Not efficacious in men, regardless of serologic status

- This vaccine currently being studied in adolescent girls prior to onset of sexual activity and HSV1 acquisition

→ results pending

Summary

- Genital herpes largely caused by HSV2, but HSV1 increasingly on the rise
- Keep a wide DDx, and swab genital lesions for confirmatory Dx
- In antenatal visits, specifically ask woman for personal and partner’s hx of genital herpes → counsel appropriately
- Screen for signs/symptoms and prodromes of genital herpes at onset of labour
Summary

- C/S recommended for 1° infection in T3 or active lesions at time of labour
- Have a high index of suspicion for neonatal herpes, esp. if mother has hx of genital herpes
- Antiviral prophylaxis at 36 weeks GA reduces risk of recurrence at time of delivery and subsequent C/S
- Acyclovir and Valacyclovir both acceptable choices