

Management of HSV infections in pregnancy

Cheryl Jones

University of Sydney, Australia
The Children's Hospital at Westmead

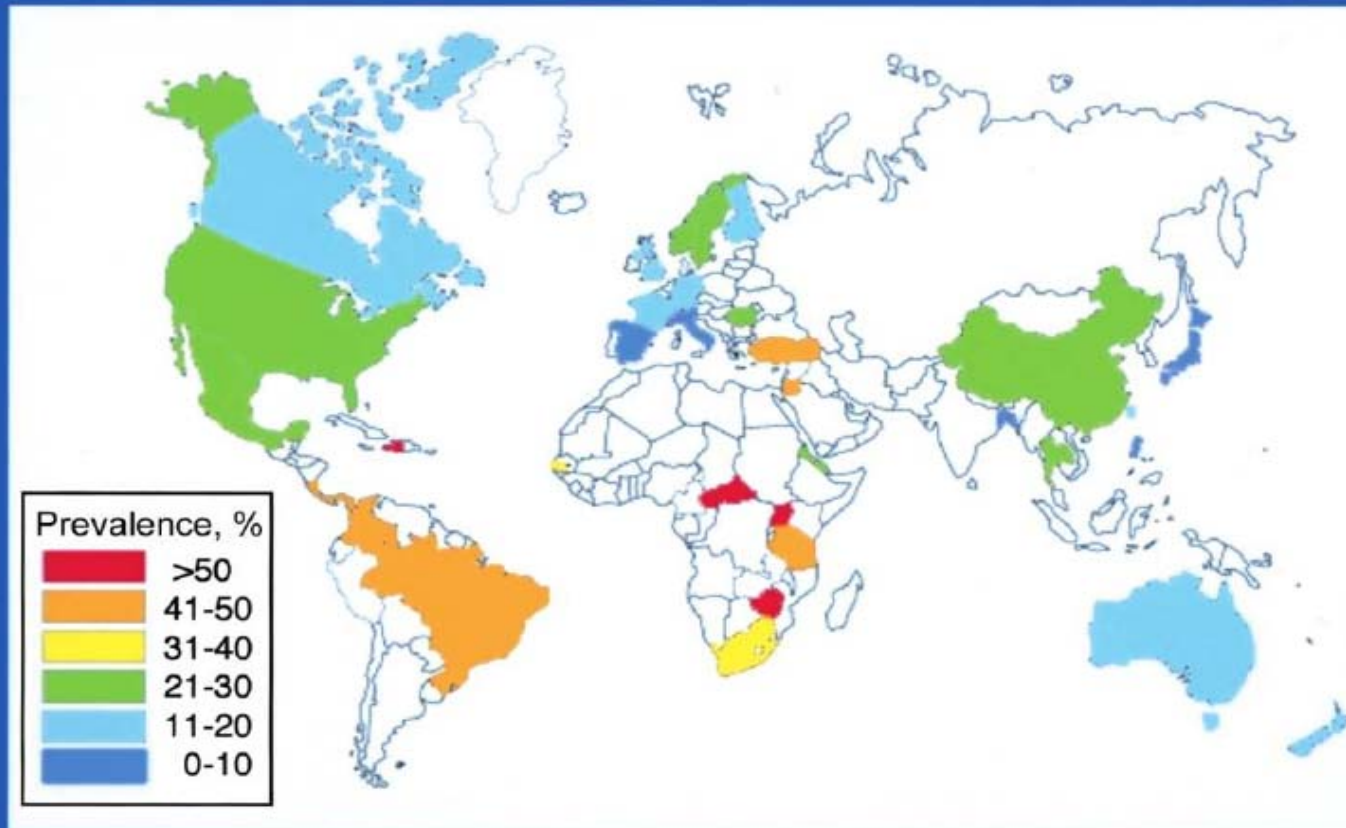




Overview

- Epidemiology of genital HSV
- Vertical transmission of HSV
- Prevention of vertical transmission
- Neonatal HSV disease

Prevalence of HSV-2 in women throughout the world (pregnant or sexually active adult women)



HSV-2 seroepidemiology



12.5%
antenatal

*Mindel et al,
2000*

HSV-1 Genital Infection

- HSV-1 seroprevalence

65% USA *Brown et al, 1997*

80% Australia *Mindel et al, 2000*

41% Japan



orolabial or genital

- Trend to acquisition of HSV-1 later in life
- HSV-1 genital infection

USA 10-30%,

Japan >50%

UK ~ >40%

In Australia?

- Greater risk vertical Txn than HSV-2
- Reflects epidemiology of neonatal HSV disease



HSV-1 genital infection in Australia

- Compared anogenital specimens HSV-1 positive NSW Virol ref lab.
- **79-88 (17,512), 89-03 (4359)**
- HSV-1 3% 1980 to 41% in 2001.
-
- 1979-1988, the Odds Ratio (OR) for an additional year was 1.24 (95% CI 1.20–1.27; $p < 0.005$).
- Female sex and age under 25 were associated with a greater proportion of HSV-1 isolates in both time periods.
- The trend seen in the proportion of IgM seropositive results reactive for HSV-1 was OR 1.36 per year (1.26–1.47; $p < 0.005$).

Hadow et al 2006

SEROPREVALENCE OF HSV IN AUSTRALIA

4000 randomly sampled sera (Ausdiab study)

		HSV-2	HSV-1
○ Age	25-34	10.2%	67%
	35-44	15.5%	75%
○ Sex	male	8.4%	71%
	female	15.6%	80%
○ Geography	city	14.4%	74-79%
	rural	8.7%	79%
○ Total		12.8%	75.7%

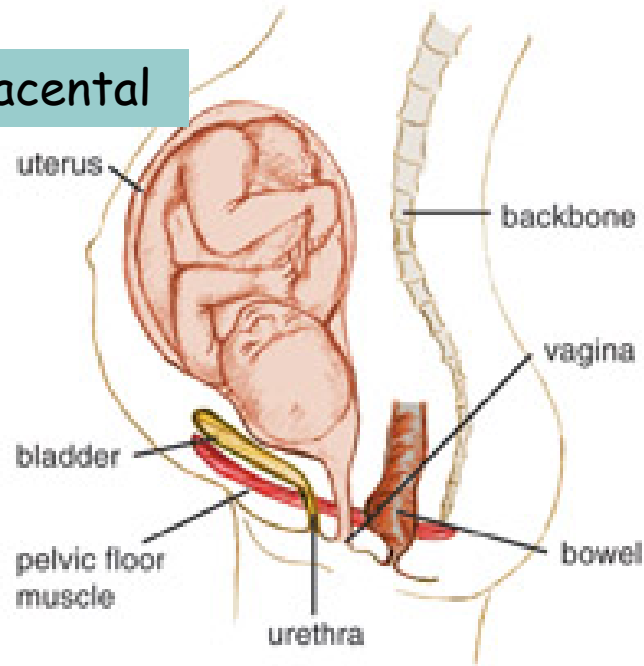


Vertical transmission of HSV

Vertical transmission = passage of (virus) from mother to fetus via

1. During pregnancy

Transplacental



Ascending

2. During delivery

3. Postnally

Close contact with mother

Questions & Answers



Breast milk



http://kidney.niddk.nih.gov/kudiseases/pubs/pregnancy_ez/

www.emorywomensprogram.org/images/QnA.jpg

C Jones RACP HSV pregnancy 00



Mode of Vertical Transmission HSV

- Congenital 1-5%
- Perinatal 85%
 - - maternal genital HSV disease
- Postnatal- 10-15%
 - infected care giver
 - Infants can breast feed unless breast abscesses

Vertical Transmission of HSV

Most genital HSV infections are asymptomatic
(Primary or Recurrent)



PERINATAL
85%

70%
No knowledge
of genital
HSV disease

Maternal HSV

Risk of transmission

Primary genital HSV

30-50%

Recurrent genital HSV

if shedding at delivery

3%

if no shedding or symptoms

~0.04%

Brown et al, 1991

Risk of transmission greatest if HSV seroconversion has not occurred prior to onset of labour



Risk factors for Vertical transmission

- Primary genital HSV disease
- HSV Serodiscordant partner
- Invasive Obstetric Procedures
 - Fetal scalp electrodes
 - Artificial ROM
 - Assisted delivery: ventouse/forceps
- Low maternal HSV-antibody levels
- Route of delivery: vaginal > c.section
- HSV serotype (HSV-1 > HSV-2)



Prevention of Vertical transmission of HSV



Possible methods to prevent/reduce vertical transmission of HSV?

- Pre/antenatal strategies to prevent maternal (genital) HSV infection
- Antenatal strategies to prevent transmission to the newborn
- Postnatal strategies to prevent infection of the newborn



Possible methods to prevent/reduce vertical transmission of HSV?

Antenatal strategies to prevent transmission to the newborn

- Counselling +/- Antenatal screening?
- Suppressive antiviral therapy for known genital HSV disease
- Caesarean section
- Reduce invasive monitoring



Antenatal screening for HSV

- Antepartum genital cultures DO NOT predict the presence of virus in the genital tract at delivery → NOT recommended

- Antenatal HSV type-specific serology?

CONTROVERSIAL

Not routinely recommended in Australia

When to perform?

Type specific HSV Ab available in Australia

Commercially Available Diagnostic Tests for Herpes Simplex Viruses

Agent	Specimen of Choice
HSV-1, HSV-2	Serum
HSV-1, HSV-2	Serum
HSV-2	Whole blood / Serum
HSV-1, HSV-2	Serum
HSV-1, HSV-2	Serum
HSV-1, HSV-2	Serum
HSV-1, HSV-2	Serum
HSV-1, HSV-2	Serum
HSV-1, HSV-2	Vesicle swab
HSV-1, HSV-2	Vesicle swab

These tests are commercially available

- Glycoprotein G
- Sensitivities: 80-98%
- Specificities: >96%
- Used:
 - counselling for sexual partners
 - Diagnosis of type of genital HSV in pregnancy
- HSV-2: usually anogenital
- HSV-1: seropositivity doesn't distinguish between orolabial and anogenital infection



Antiviral therapy during pregnancy

- Used in two ways
 - Rx severe/disseminated disease/ presumed primary infection
 - Suppress recurrences in third trimester



Safety of Antivirals in Pregnancy

- ACV, VACV : Category B drugs
- Famciclovir not used due to concerns re teratogenicity in animal studies
- CDC review of Aciclovir and Valaciclovir Pregnancy Registry **MMWR 2002**
 - “insufficient data to recommend their use in pregnancy, although no adverse fetal effects have been reported”
- Pharmacokinetics of use in pregnancy:
 - ACV, VAC distribution in pregnant women like non pregnant adult
 - Aciclovir concentrated in amniotic fluid/ breast milk
 - no evidence of preferential accumulation of either drug in fetus at delivery or toxicity in infant at follow up**Kimberlin et al, 1998**
- Balance potential risk to fetus with potential benefits of Rx

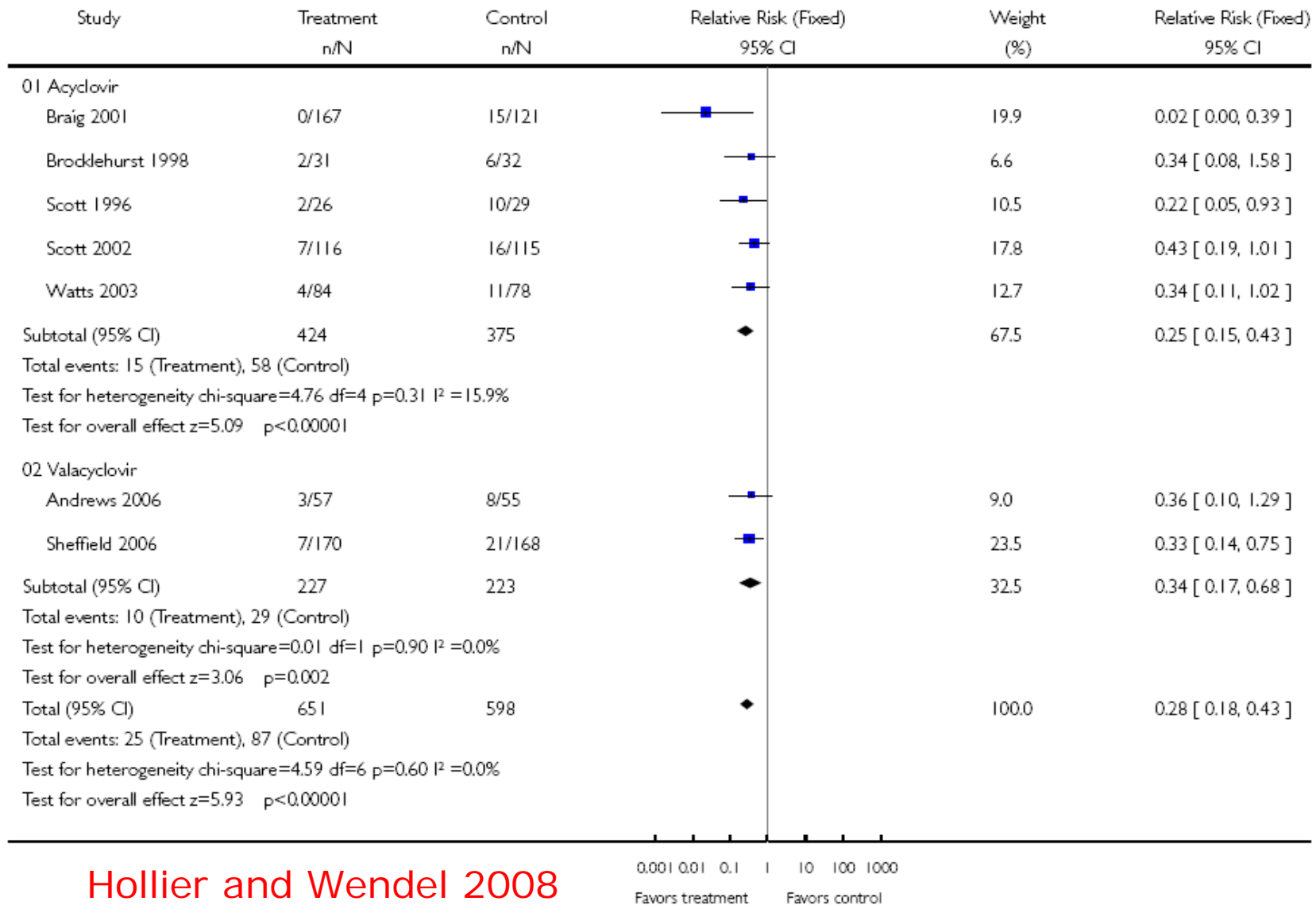
Antivirals for recurrent genital HSV in pregnancy

Authors/ Drugs	No. enrolled/ start date	Outcomes measured/ ?significant		
		Genital Clinical recurrence	Virus in genital tract	C. Section rate
<i>Stray-Pedersen 1990, 1998</i> Aciclovir 200 mg 4x/d V. No Rx	46A/ 46 NR 39Wk	√	√	√ / sig. ↓
<i>Brocklehurst et al. 1998</i> Aciclovir 800mg/d V. Placebo	31A/ 31P 39 Wk	√		√
<i>Braig et al 2001</i> Aciclovir 200mg 4x/d V. Placebo V. Hx gen Herpes and No Rx	167A/121/ 201 NoRx	√	√	√
<i>Watts et al. 2003</i> Aciclovir 400mg tds V. Placebo	84A/ 78P 36 Wk	√	√/ sig. ↓	√
<i>Scott et. al. 2002</i> Aciclovir 400mg tds V. Placebo	116A/115P 36 wk	√	√/ sig. ↓	√
<i>Sheffield et. al. 2006</i> Valaciclovir 500mg bd V. Placebo	170V/ 168P 36 wk	√	√/ sig. ↓	√/ sig. ↓
<i>Andrews et al. 2006</i> Valaciclovir 500 mg bd V. Placebo	57 V/ 55P 36 wk	√	√/ sig. ↓	√

Antivirals for primary HSV in pregnancy

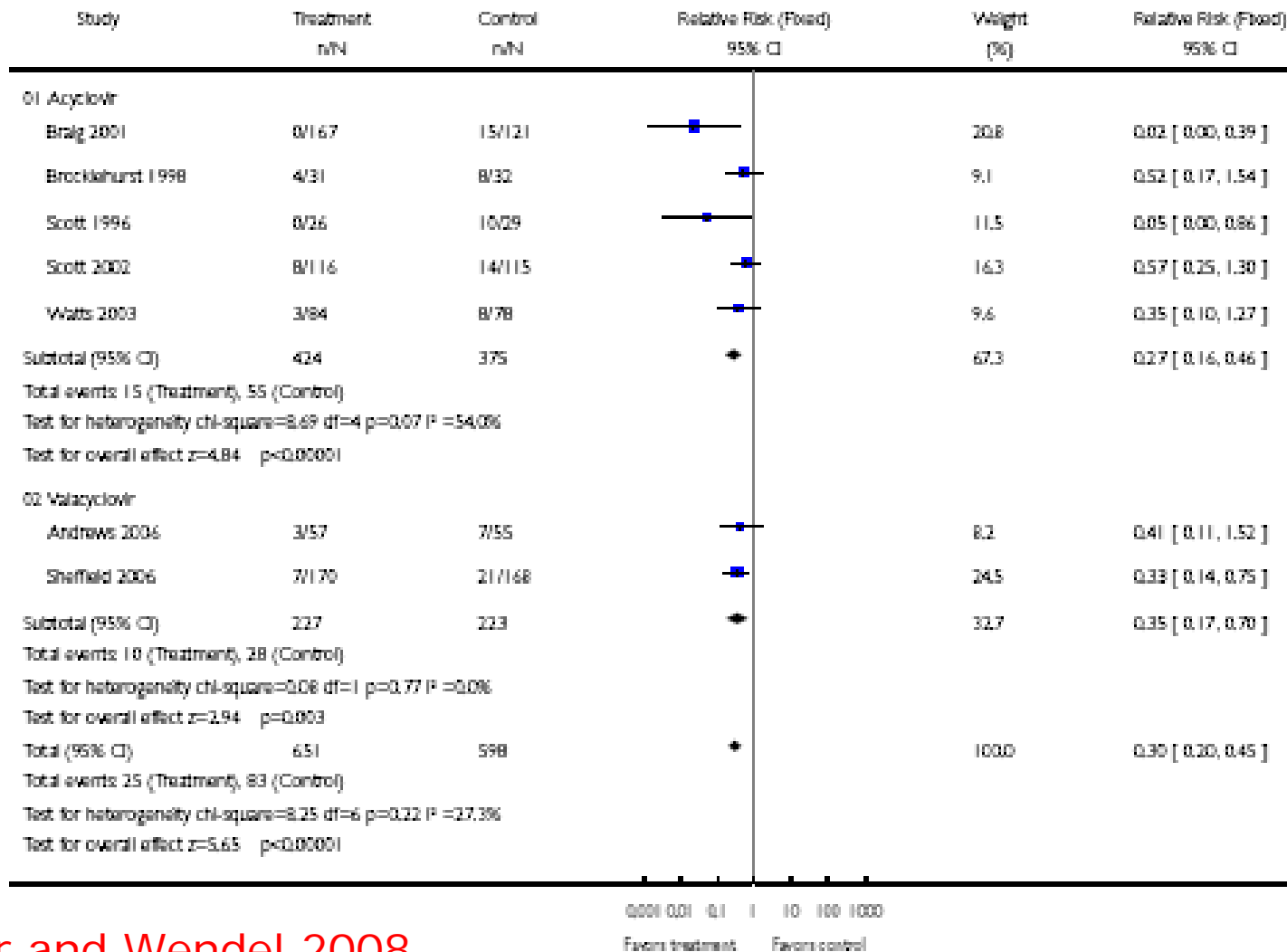
Authors/ Drugs
Scott et al 1996 Aciclovir 400 mg tds open label\from 36 weeks
Stray-Pedersen et al 1990 Aciclovir 200 mg 4x/day from 36 weeks
Scott et al Aciclovir 400 mg po tds from 2-3 weeks before delivery
<i>Sheffield et. al.</i> Valacyclovir500mg bd po vs. Placebo from 36 weeks- included in larger trial with recurrent HSV

ACV and VACV reduce clinical genital herpes recurrence at delivery



Hollier and Wendel 2008

ACV and VACV reduce Caesarean section for genital herpes



Hollier and Wendel 2008

Maternal Antivirals to prevent Neonatal HSV at delivery

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Antenatal antiviral prophylaxis versus placebo, Outcome 01 Neonatal herpes

Review: Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection

Comparison: 01 Antenatal antiviral prophylaxis versus placebo

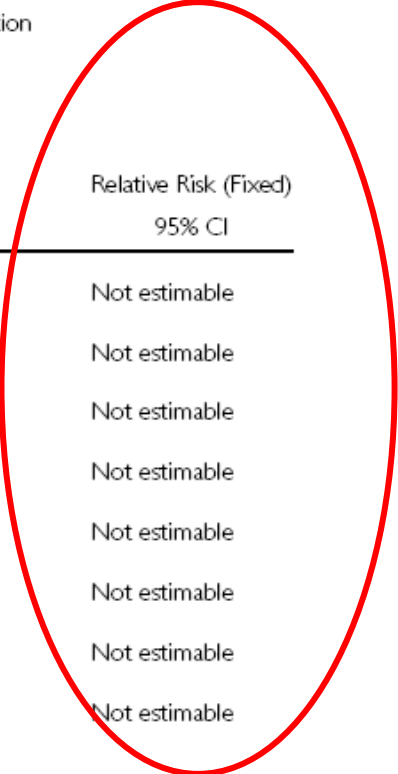
Outcome: 01 Neonatal herpes

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Andrews 2006	0/57	0/55		0.0	Not estimable
× Braig 2001	0/11	0/11		0.0	Not estimable
× Brocklehurst 1998	0/11	0/11		0.0	Not estimable
× Scott 1996	0/27	0/27		0.0	Not estimable
× Scott 2002	0/116	0/115		0.0	Not estimable
× Sheffield 2006	0/170	0/168		0.0	Not estimable
× Watts 2003	0/84	0/78		0.0	Not estimable
Total (95% CI)	646	594		0.0	Not estimable

Total events: 0 (Treatment), 0 (Control)
 Test for heterogeneity: not applicable
 Test for overall effect: not applicable

0.01 0.1 1 10 100
 Favors treatment Favors control

Insufficient power to determine



Hollier and Wendel 2008



Valacyclovir Prophylaxis to Prevent Recurrent Herpes at Delivery

- Valaciclovir 500mg qid significantly reduce viral shedding and clinical recurrences at delivery
- valaciclovir decreased the no of caesarean deliveries performed for HSV, (13% to 4%, $p = .009$). It should be noted that even with valaciclovir, some women still have recurrences and may require caesarean section.
- valaciclovir prophylaxis was tolerated well in late pregnancy, had no adverse effects on the neonate and significantly reduced clinical recurrences at delivery, laboratory detection of HSV at delivery, and caesarean delivery for HSV.
- 11 women would need to be treated with valaciclovir to prevent 1 caesarean delivery for HSV.

Sheffield et al, O & G, 2006



Antivirals for HSV in pregnancy

- Aciclovir 400mg tds or VAC 500mg bd
 - symptomatic 1% /first episode
 - disseminated HSV IV ACV
 - recurrences [maternal symptomatology]
 - recurrences [frequent] suppressive Rx36w to term to ↓ LUSCa

- IV antivirals during labour: await results of RCT. NO data yet

Caesarean section to reduce vertical transmission of HSV

Type of delivery		OR (95% CI)	P value	Adjusted OR (95% CI)
Cesarean	1/85 (1.2)	0.14 (0.02-1.08)	.047	0.14 (0.02-1.26)
Vaginal	9/117 (7.7)			

Table 2. Delivery Route and Acquisition of Neonatal Herpes in Women With Herpes Simplex Virus Isolated From the Genital Tract, Stratified by Presence of Lesions

	Neonatal Infection	No Neonatal Infection	Total
Women with lesions present at delivery			
Cesarean	0	60	60
Vaginal*	0	14	14
Women with subclinical viral shedding			
Cesarean	1	24	25
Vaginal	9	94	103
Overall			
Cesarean	1	84	85
Vaginal	9	108	117
Total	10	192	202

*Lesions noted immediately postpartum or too late for cesarean delivery.

Brown et al, JAMA 2003



Caesarean Section to prevent HSV vertical transmission

- Indicated if lesions in genital tract at delivery or recent proven primary genital HSV

- but consider.. Site/ severity/ROM

- ROM: Duration of rupture of membranes- Approx. <4-6 hours. Only study -small nos, poor quality study- Nahmias et al, 1987
- Not completely protective: up to 30% of APSU cases of neonatal HSV disease were delivered by C. section



Possible methods to prevent/reduce vertical transmission of HSV?

- Pre/antenatal strategies to prevent maternal (genital) HSV infection
- Antenatal strategies to prevent transmission to the newborn
- Postnatal strategies to prevent infection of the newborn



Possible methods to prevent/reduce vertical transmission of HSV?

Pre/antenatal strategies to prevent maternal (genital) HSV infection

- Counselling +/- Antenatal screening?
- Abstinence/Barrier methods?
- Topical microbicides?
- Suppressive antiviral therapy to HSV infected partner
- Prophylactic vaccination against genital HSV



Abstinence/Barrier Methods

- Counsel re: (from 28 weeks)
 - Condom use
 - Abstinence in late pregnancy
 - Avoidance of orogenital contact
- Efficacy? *Kulhanjan et al NEJM 1992*
 - Screened 180 couples for HSV-Ab
 - 10% (18) women HSV seroneg/ seropos partners
 - Counselling re abstinence
 - 7/18 continued to have unprotected sex



Suppressive antiviral Rx in partner

- ACV, VACV, FAMV: Studies of serodiscordant partner transmission, but none specific in pregnancy
- Requires type specific Ab testing of women and partner
- Give to seropositive partner from 28 weeks.



Possible methods to prevent/reduce vertical transmission of HSV?

- Pre/antenatal strategies to prevent maternal (genital) HSV infection
- Antenatal strategies to prevent transmission to the newborn
- Postnatal strategies to prevent infection of the newborn
 - IV ACV to newborn high risk of exposure?
e.g. offspring of women with confirmed genital herpes or unknown status and vaginal delivery through active herpes
Recommended by many experts but no data about efficacy



1. Mx genital herpes in pregnancy & labour Hx- *prior infection*

- Pregnancy
 - Counsel low risk of vertical transmission, how to further reduce risk
 - No role serial genital cultures
 - Consider suppressive antiviral therapy from 36 weeks
 - Discuss delivery options
- Labour
 - Careful speculum exam
 - Lesions visible & ROM <6 hours: C. section relative indication
 - Vaginal delivery: invasive monitoring for defined obstetric indications only

2. No prior Hx genital herpes *Presents antepartum*

- Antiviral Rx to treat initial infection:
 - IV if disseminated/severe
 - Effect on reducing risk of intrauterine transmission?
- Characterise type of infection (primary vs recurrent)
 - type specific genital culture/
HSV type specific serology

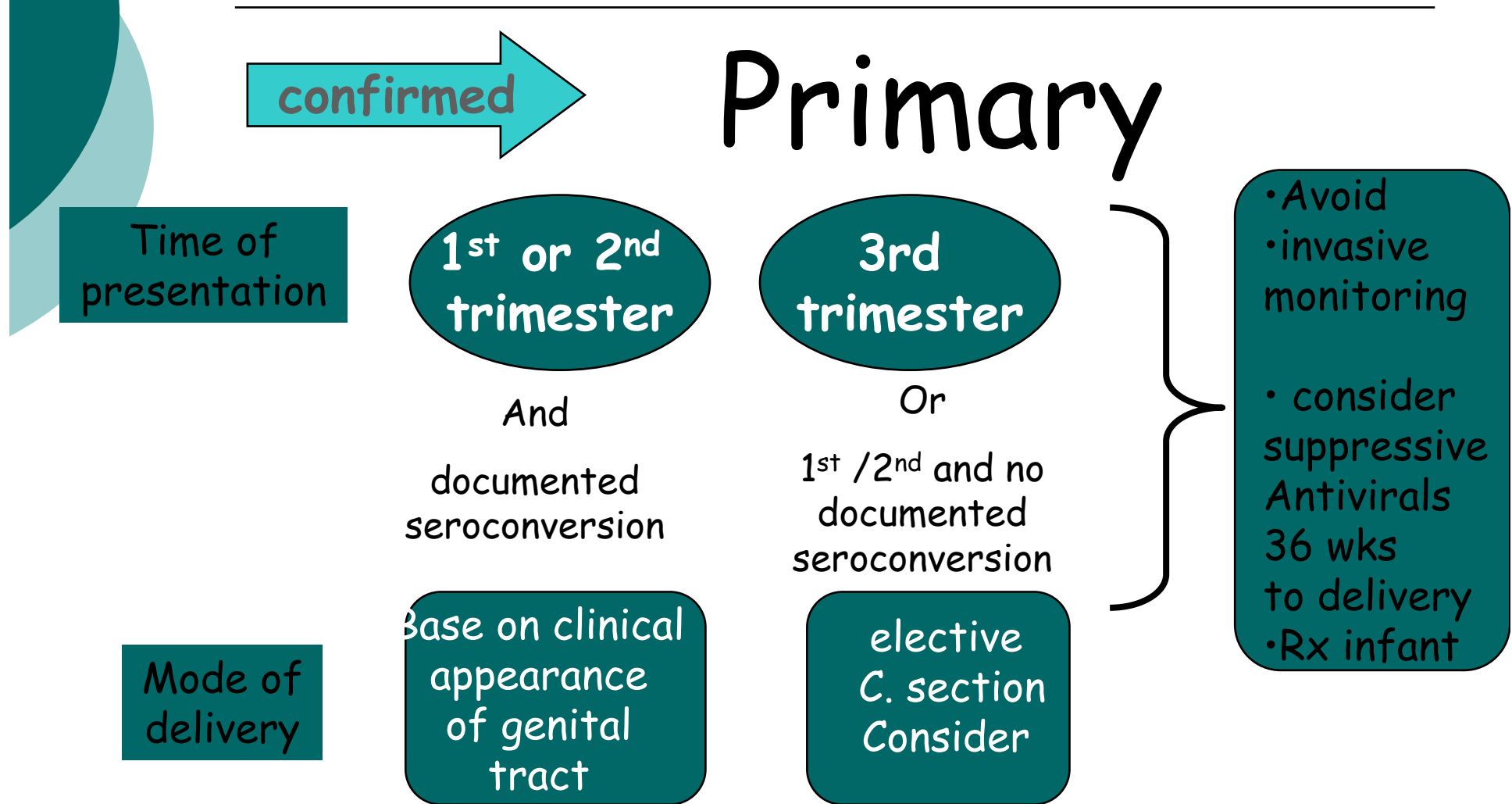
confirmed

Reactivation

C Jones RACP HSV pregnancy 08

Counsel
Mx as Recurrent
genital HSV

2. No prior Hx genital herpes *Presents antepartum*



Summary-Genital herpes in pregnancy/ Neonatal HSV

- Primary - 1st, 2nd trimester
 - Rx ACV if indicated - no evidence of fetal risk
 - Frequent recurrence
 - ? ACV prophylaxis 400 mg tds
- Recurrences (<3% transmission)
 - no active lesions at term - vaginal delivery
 - active lesions - LUSCS (unless MR >6 hr)
- Primary - 3rd trimester
 - Rx mother and infant: Risk of preterm delivery; transmission (40%)
 - LUSCS (investigate +/- treat infant)



Neonatal HSV infection



3. No prior Hx genital herpes Presents intrapartum

- Elective C. section to reduce risk of vertical transmission
- Collect type specific serology and genital culture
- Avoid invasive obstetric procedures
- Collect surface swabs on infant for viral culture- **start immediate** empiric aciclovir on infant ?

Neonatal HSV Infection

Clinical manifestations?

- Skin, eye, mouth lesions
- Encephalitis
- Disseminated infection
- Pneumonitis





Neonatal HSV

Predictors of Mortality

Prospective study: 202 infants with confirmed neonatal HSV infection

	RR
● ↓ Level of consciousness at start of Rx	5.2
● DIC with disseminated disease	3.8
● Prematurity	3.7
● HSV pneumonitis in disseminated disease	3.6

Whitley et al, NEJM, 1991



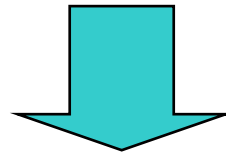
Mx neonatal HSV

- 3 scenarios
 - Suspicious clinical signs
 - Infant born to women with active genital herpes at delivery
 - Infant born to women with Hx recurrent genital HSV disease

Neonatal HSV- clinical signs

vesicles/bullae, seizures, unexplained sepsis (Bld cx neg, no response to Abx), resp distress in Term baby d3+, DIC, hepatitis, thrombocytopenia

irrespective of maternal Hx:



Ix & commence empiric IV aciclovir immediately



Neonatal HSV- Ixns

- skin lesion, nose, throat,
conjunctiva swab: Cx +/- PCR
- skin lesion: indirect IF (rapid)
- CSF exam
 - wcc, pr, gluc, HSV PCR, cx, viral cx
- CNS imaging
- Blood: FBC, LFTs, coags,
- serology: little role to play

Survival ?

- In Australia: 25% acute mortality
 - APSU HSV study

- Gestation of infants that died?
 - < 37 weeks 85%*

- Category of disease

**1 Death of preterm infant at 56 days ? due to other cause*

SEM	*5%
Disseminated	50%
I/uterine death	5%
Pneumonitis	39%
CNS alone	0%



Neonatal HSV- delivered through HSV birth canal

- Mother Primary or Recurrent HSV?
- Known primary or unknown
 - investigate & commence immediate treatment IV ACV ? How long- 10 days : Cx neg, 14 days Cx +ve and no CNS signs/CSFPCR neg; 21 days if CSF PCR pos or develops CNS signs
- Recurrent disease? surface swabs at 24 hours vs watch closely and investigate and Rx if signs...severe disease: Rx if +Ve or clinical signs- full Ix and Rx (unless severe disease)



Neonatal HSV

Hx recurrent genital HSV

- Inspection and high vaginal swab at delivery
- Risk to infant negligible if Cx/PCR neg
- Educate parents about signs of HSV disease
- surface swabs on infant at 24 hrs if high parental concern?



Neonatal HSV infection

Management of recurrences

CONTROVERSIAL

- Role of suppressive therapy
 - Not established yet
 - Ph 2 trial: Oral aciclovir 300mg/m²/dose 3 times/day- prevented HSV recurrence after CNS disease, effect on CNS outcome unknown, neutropenia in 46%- Trial ongoing
- Investigations:
 - Include LP to exclude CNS recurrence
 - IV aciclovir therapy for 14 days if -ve, 21 days if +ve?
 - Until when? 6 months
- Late CNS recurrences reported
- Preterm infant developed CNS recurrence on oral ACV

Aciclovir therapy for neonatal HSV disease- past recommendations

	MORTALITY (Neonatal)	
○ Pre antiviral era	CNS	50%
	Disseminated	85%
○ Low dose aciclovir (10mg/kg/dose IV q8H) 10-14 d	CNS	14%
	Disseminated	54%

(Whiteley et al, NEJM, 1991)

↓ CNS relapse: ↑ duration to 21 days (CNS or disseminated)



Current aciclovir dose recommendations: neonatal HSV disease

- Aciclovir 20mg/kg/dose IV given 8th hourly
 - Duration:
 - 21 days if encephalitis/ disseminated infection or LP not performed
 - 14 days for disease localised to skin, eye or mouth

Kimberlin et al, Pediatrics, 2001

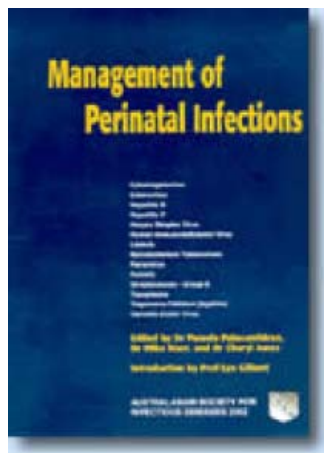
Management of Perinatal Infections

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http://www.racp.edu.au/asid/resources_perinatal.htm

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