REVIEW ARTICLE

Drugs 2009; 69 (4): 421-434
0012-6667/09/0004-0421/$55.55/0

Vertical Transmission of Genital Herpes
Prevention and Treatment Options

Cheryl A. Jones[1,2]

1 Discipline of Paediatrics and Child Health, University of Sydney, Sydney, New South Wales, Australia
2 Centre for Perinatal Infection Research, The Children's Hospital at Westmead, Westmead, New South Wales, Australia

Contents

Abstract

Herpes simplex virus (HSV) transmitted from mother to child around the time of delivery can cause potentially fatal disease in the newborn. Women who experience their first genital HSV infection in pregnancy are at the highest risk of transmitting the virus to their newborn. Efforts to prevent

vertically transmitted HSV disease can be directed in the following three ways: (i) prevent maternal genital HSV infection; (ii) prevent transmission during pregnancy and delivery; or (iii) postnatally prevent disease in an exposed newborn. Oral aciclovir and valaciclovir given prophylactically in late pregnancy have been shown to limit clinical recurrence of genital herpes, shedding of HSV at delivery and the rate of caesarean delivery for past HSV disease. However, there are insufficient data to determine the effect of oral antiviral prophylaxis in pregnancy on neonatal HSV disease. Neonatal HSV disease should always be treated with systemic antiviral therapy. There is currently no vaccine licensed to prevent genital herpes, although a number show promise in clinical trials. The role of intrapartum antiviral therapy and postnatal strategies to prevent neonatal HSV disease require further evaluation.

1. Herpes Simplex Virus (HSV) Biology and Epidemiology

Herpes simplex virus (HSV) is a ubiquitous pathogen that causes a large burden of disease worldwide, particularly in the immunocompromised and the newborn.[1] There are two HSV serotypes: (i) HSV type 1 (HSV-1), which mainly causes orolabial and CNS infections; and (ii) HSV type 2 (HSV-2), which is the major cause of genital HSV disease. However, both serotypes can cause HSV disease at either end of the body. HSV establishes life-long latency in the sensory ganglia after acute infection, often followed by frequent reactivation and shedding of infectious virus from the site of infection, which is often subclinical. These properties, coupled with the capacity of some HSV proteins to modulate the host's immune response,[2,3] are a major hindrance to the success of public health measures to prevent HSV transmission.

Genital herpes has recently been shown to play a major role in the HIV pandemic, especially in developed countries, where individuals with genital HSV infection display an increased risk of HIV infection after exposure, and an increased rate of HIV transmission to others (including by vertical transmission) once infected.[4,5] Whether HIV-positive women have an increased risk of vertical transmission of HSV to their offspring has not been fully defined.

One of the most devastating sequelae of genital HSV disease is infection in the newborn. Although an uncommon complication of genital herpes, neonatal HSV disease carries high mortality and morbidity.[6] This review provides an update on the natural history of neonatal HSV disease, methods of diagnosis, and current strategies for treatment of primary neonatal infection and reactivation. It primarily focuses on pharmacological strategies to prevent vertical transmission of HSV, in particular, antiviral therapy for pregnant women with genital herpes and their partners. A summary of non-pharmacological methods is also provided.

2. Natural History of Neonatal HSV Disease

2.1 Incidence and Epidemiology

Reported rates of neonatal HSV disease and the predominant serotype responsible vary around the world. In the US, the reported incidence is 20–60 cases per 100 000 live births.[6-8] The reported incidence is lower in the UK, Australia and Japan, with reported national averages of 1.5–4 cases per 100 000 live births.[9-11] Differences in reported rates may partly reflect differences in reporting systems, but may also reflect differences in the seroprevalence of each HSV serotype, differences in obstetric practices and potentially differences in sexual practices.[12] Both HSV-1 and -2 can cause neonatal HSV disease. In the US, approximately 70% of cases are due to HSV-2, whereas in Australia, the UK and Japan, HSV-1 causes ≥50% of infections.[6,10,11]

2.2 Routes of Transmission

The commonest route by which the newborn acquires HSV (85%) is by passage through an infected birth canal. The remainder, approximately 10–15% of neonatal infections, are acquired postnatally by contact with an infected caregiver, while 5% of cases are true intrauterine infections, which carry a different spectrum of disease.[13-15] HSV typically enters through the mucoepithelium of the eye or nasopharynx of the neonate, but infection can also occur after ingestion or inhalation of infected maternal secretions or at the site of scalp skin trauma from the use of invasive obstetric devices such as scalp electrodes, ventouse/vacuum extractors or forceps.[13] Intrauterine infection can occur from transplacental transmission after maternal viraemia or after an ascending infection from the cervix.

2.3 Clinical Presentation of Neonatal HSV Disease

Perinatal HSV disease in the newborn manifests in the following four ways: (i) as disease localized to the skin, eye and mouth (SEM disease); (ii) as encephalitis alone; (iii) as a disseminated multi-organ system infection with or without encephalitis; or (iv) as isolated pneumonitis.

Recent reviews from around the world indicate that approximately 50% of infants present with SEM disease.[6,11] This typically presents at approximately 10–11 days of age and carries a very low to no risk of mortality, although without appropriate antiviral therapy infection will spread to the CNS or viscera in up to 70% of these infants and just under half will have late-onset neurological impairment.[13] Around 25–30% of infants present with HSV encephalitis. Most of these infants do not have cutaneous manifestations. Signs at presentation are therefore nonspecific, such as temperature instability, poor feeding and seizures in the second or third week of life.[13] Neonatal HSV encephalitis has a mortality rate of up to 50% if untreated, but mortality is significantly reduced by the early introduction of antiviral therapy.[16,17] However, HSV encephalitis carries a high risk of long-term neurological sequelae in survivors.[13,16,17]

The remaining 25–30% of infants with multi-organ HSV disease typically present in the first week of life with disseminated intravascular coagulation, respiratory distress and/or jaundice. Once again, cutaneous manifestations of HSV are often absent. Mortality of this form of infection is high, i.e. approximately 30% with prompt initiation of antiviral therapy ranging up to 85% in the absence of therapy, and up to 30% will develop long-term sequelae.[16,17] A particularly virulent form of multi-organ infection is neonatal HSV pneumonitis, which typically presents at about 3–7 days of life as respiratory distress in a term infant who is otherwise well at birth.

HSV can also rarely be transmitted from the mother to the fetus via the placenta.[15] Intrauterine HSV infection is characterized by the presence of skin, eye and neurological manifestations at birth, including microcephaly, skin scarring and microphthalmia.

2.4 Risk Factors for Transmission

The maternal risk factors for vertical transmission of HSV are listed in table I.

2.4.1 Type of Maternal Genital Infection/Virus in the Genital Tract

Women who acquire their first genital HSV infection in pregnancy have a greater risk of

Table I. Risk factors for vertical transmission of herpes simplex virus (HSV)

Risk factor	References
Virus in genital tract at delivery	8
First genital HSV disease in late pregnancy	18,19
HSV serodiscordant partner	20
Low maternal HSV type-specific antibody at delivery	21,22
Invasive obstetric procedures[a] at delivery	8
Vaginal delivery with infectious HSV in genital tract	8
HSV type 1 genital HSV disease	8,19
HIV co-infection	23

a Scalp electrode, forceps, ventouse extractors.

transmitting HSV to their infant during delivery than women who have recurrent genital herpes. Primary genital HSV infection late in pregnancy is associated with attack rates of 30–60% for neonatal HSV infection compared with 1–3% after reactivation of genital herpes.[7,8,18] One of the largest studies defining risk factors for maternal transmission of HSV analysed intrapartum viral shedding in the birth canal of almost 40 000 pregnant women in the US.[8] HSV in the genital tract was detected in labour in 0.5% of women, 5% of whom (10 of 202) had infants with neonatal HSV infection compared with 0.02% (6 of 39 821) of women with negative genital cultures. Of those who had type-specific serology performed, 85% were seropositive for the HSV serotype isolated on genital culture at delivery, suggesting recurrent genital herpes, and 15% had serological evidence of their first episode of genital herpes. Transmission to the newborn was reported in 8 of 26 (30%) first episodes of genital herpes compared with 2 of 151 (1.3%) episodes of shedding from recurrent herpes.[8]

2.4.2 Presence of Maternal HSV Type-Specific Antibody at Delivery

One reason for the lower rate of vertical transmission by women with recurrent genital herpes is that they have transferred neutralizing, HSV type-specific antibody to their fetus. Women who seroconvert to HSV well before the onset of labour appear to have a lower risk of having an infant with neonatal HSV disease than women who acquire their first infection in late pregnancy.[21] Prior maternal HSV-1 antibody appears to provide little protection against the acquisition or vertical transmission of genital HSV-2 infection.[8,19] The level of transferred HSV type-specific antibody can also influence the outcome of neonatal HSV disease; infants with mild infections have higher titres of transplacentally derived antibody than infants with severe disease who have lower titres.[22]

2.4.3 Serotype of Maternal Genital Infection

Recent studies suggest that HSV-1 in the genital tract may be transmitted more readily to the infant than HSV-2. Prospective analysis of over 40 000 deliveries in the US suggested HSV-1 isolation at delivery carried an almost 17-fold greater risk of vertical transmission than HSV-2 (95% CI 4.1, 65).[8] Pooled analyses from 78 cases of neonatal HSV disease and known maternal HSV serostatus in the US and Sweden suggested that during reactivation, HSV-1 appears more readily transmissible to the neonate than HSV-2.[19]

2.4.4 Invasive Obstetric Procedures

If virus is in the genital tract, the use of fetal scalp electrodes increases the risk of neonatal HSV disease.[7,8] This has been extrapolated to the use of other invasive procedures such as artificial rupture of membranes where the scalp is scarred, and the use of forceps or vacuum extractors.

2.4.5 Serodiscordant Partner

Studies have shown that an HSV seronegative woman is at risk of acquiring genital herpes during pregnancy if her partner is HSV seropositive.[20] This is particularly true for an HSV-2 seronegative woman with an HSV-2 seropositive male partner. However, genital infection can be acquired from an HSV-1 seropositive partner by orogenital contact or by genital contact if the partner has genital herpes due to HSV-1. The high frequency of subclinical shedding of HSV means that transmission can occur even in the absence of identifiable lesions or symptoms such as tingling.

2.4.6 HIV Co-Infection

Another possible risk factor for vertical transmission of HSV is HIV co-infection. HSV-2 infection has been shown to be a risk factor for the acquisition of HIV in adults,[24] at least in some parts of the world. One recent case control study from the US reported that vertical transmission of HIV was not increased in the presence of maternal HSV-2 seropositivity,[25] whereas another recent study, from Thailand, showed a 2- to 3-fold increased risk of perinatal HIV transmission in HSV-2 seropositive women compared with HSV-2 controls (adjusted odds ratio 26; 95% CI 1.0, 6.7).[23] The effect of HIV on HSV vertical transmission has not been fully defined. Importantly, the prevalence of HSV-2 shedding in African HIV-positive women is greater than in HIV-negative female patients, and

the risk of HSV reactivation in pregnancy is increased (8% vs 1–2%).[25]

3. Diagnosis of Neonatal Herpes

As the symptoms and signs of neonatal HSV infection are nonspecific, child health providers must have a high index of suspicion and commence empirical systemic antiviral therapy while awaiting confirmation from laboratory tests. Laboratory tests required in the evaluation of an infant are listed in table II.

Cerebrospinal fluid (CSF) should be obtained from all infants with suspected neonatal HSV disease for polymerase chain reaction (PCR), cell count and biochemistry. Some laboratories will also assay CSF for viral culture, although the yield is lower than for PCR. Urine and surface swabs from any skin lesion, conjunctiva, nasopharynx or rectum should be collected for viral culture and/or immunofluorescence and/or PCR. HSV DNA can also be detected by PCR in the blood of up to 60–70% of infants with neonatal HSV disease.[26] Rapid confirmation of HSV infection can be obtained by direct immunofluorescence of swabs taken from the deroofed base of a lesion and plated onto a glass slide. A positive result provides rapid confirmation of infection, although a negative result does not exclude the diagnosis.

Table II. Investigations for suspected neonatal herpes simplex virus (HSV) infection

CSF
Cell count
Biochemistry (protein, glucose)
Virological culture
PCR
Blood
Blood count
Coagulation studies
Liver function tests
PCR
Skin lesions
Direct immunofluorescence
Viral culture[a]
PCR
Urine and surface swabs[b]
Viral culture[a]
PCR
Other tests
Cerebral imaging: head ultrasound, MRI or CT scan (if seizures)
EEG
Chest radiograph

a Swabs for viral culture must be placed in viral transport medium, and transported at 4°C to the laboratory.

b Nasopharyngeal aspirate, umbilical swab, eye swab, rectal swab.

CSF = cerebrospinal fluid; **MRI** = magnetic resonance imaging; **PCR** = polymerase chain reaction.

While PCR assessment of CSF for HSV DNA is the diagnostic method of choice for herpes encephalitis, false negative results do occur.[27] CSF viral culture can be positive in up to 20% of infants with neonatal HSV disease, in contrast with the low yield of culture from older children or adults with HSV encephalitis.[27,28] In contrast with viral culture, the sensitivity of PCR appears to be lower for neonatal herpes than for adults with HSV encephalitis: reported sensitivities range from 71% to 100% in neonates versus 98% in adults (compared with brain biopsy specimens as the gold standard).[29] The rate of detection of HSV DNA in the CSF of infected neonates decreases after 1 week of antiviral therapy.[30] HSV viral load >100 copies/mL is associated with poor neurological outcome in adults.[31] Similar studies have yet to be performed in infants. Most experts recommend that a PCR analysis be performed on the CSF at the end of therapy to confirm the absence of HSV DNA.

There is no role for performing serology on the infant in the acute diagnosis of HSV infection in the neonate. Development of HSV type-specific IgM responses in neonates is too slow to guide therapy.

4. Treatment of Neonatal HSV Disease

Empirical intravenous aciclovir therapy at a dosage of 60 mg/kg/day divided into three doses and given by slow infusion should be promptly commenced at the time neonatal HSV disease is first considered, to reduce the risk of progression of disease. Current recommendations for aciclovir therapy for the treatment of proven neonatal HSV

disease[32] are listed in table III. The duration of therapy will depend on the results of investigations and the type of neonatal HSV disease. Studies that have led to the current recommendations are discussed in this section. Infants with HSV eye disease should be treated with topical ophthalmic antiviral preparations in addition to systemic antiviral therapy.

4.1 Trials of Antiviral Therapy for the Treatment of Neonatal HSV Disease

The first randomized controlled trial assessing the efficacy of antiviral therapy for neonatal HSV disease was reported by Whitley and colleagues[33] in 1980 and compared intravenous vidarabine with placebo. Sixty-three newborns with laboratory-confirmed HSV infection were randomized to receive either intravenous vidarabine (15 mg/kg/day over 12 hours for 10 days) or placebo. The mortality of all forms of neonatal HSV disease was reduced by vidarabine treatment from just over 50% to approximately 30%, with the greatest change seen in infants with disseminated infection or encephalitis. A later study compared intravenous aciclovir with vidarabine.[17] The study enrolled 210 infants who received vidarabine (30 mg/kg/day over 12 hours) or intravenous aciclovir (30 mg/kg/day divided into three doses). The two drugs were equally efficacious at reducing mortality and morbidity when the differences in categories of disease were taken into account.

Table III. Aciclovir therapy for the treatment of neonatal herpes simplex virus (HSV) disease[32]

Type of neonatal HSV disease	Intravenous dose and duration of therapy[a,b]
Suspected (empirical therapy)	60 mg/kg/day in 3 equally divided doses every 8 h, given as 1-h infusion until diagnosis and type of disease confirmed
Skin, eye, mouth[c]	60 mg/kg/day in 3 equally divided doses every 8 h, given as 1-h infusion for 14 days
CNS	60 mg/kg/day in 3 equally divided doses every 8 h, given as 1-h infusion for 21 days
Disseminated	60 mg/kg/day in 3 equally divided doses every 8 h, given as 1-h infusion for 21 days
LP not performed at diagnosis	60 mg/kg/day in 3 equally divided doses every 8 h, given as 1-h infusion for 21 days

a Maintain hydration and monitor neutrophil counts.

b Adjust dose for renal function and preterm gestation.

c Cerebrospinal fluid HSV polymerase chain reaction should be negative; biochemistry and cell count should be normal.

LP = lumbar puncture.

Other systemic antiviral agents with efficacy against HSV (foscarnet and cidofovir) have not been evaluated in clinical trials for the treatment of neonatal HSV disease, largely because of toxicity and, for cidofovir, the lack of an intravenous preparation. Foscarnet is recommended for the treatment of neonatal HSV disease caused by aciclovir-resistant strains, which is a relatively rare event.[34] Oral aciclovir preparations should not be used in the treatment of neonatal HSV disease because of the low bioavailability and the need to achieve high CNS antiviral concentrations to inhibit viral replication. There are currently no data to support the use of newer oral antiviral preparations with better bioavailability for the treatment of neonatal HSV disease (e.g. valaciclovir, famciclovir).

4.2 Dose and Duration of Aciclovir Therapy for the Treatment of Neonatal HSV Disease

Intravenous aciclovir has become the standard therapy for this disease because of the ease of administration and the relative toxicity of systemic vidarabine. The recommended dose and duration of aciclovir therapy has increased to 60 mg/kg/day in three equal doses for 14 days (for SEM disease) to 21 days (for disseminated infection and/or encephalitis) to reduce disease progression and further reduce mortality from disseminated infection or encephalitis. These changes are based on an open-label evaluation of infants receiving 45 or 60 mg/kg/day for 21 days compared with historical data for infants receiving the low-dose short course therapy that showed significantly increased survival for infants with disseminated HSV disease and reduced overall neurological sequelae at 12 months of age in infants who received high-dose therapy.[32] Infants receiving aciclovir therapy should be kept well hydrated to avoid renal toxicity, and their neutrophil counts and renal function should be monitored while receiving therapy.

4.3 Suppressive Antiviral Therapy to Prevent Long-Term Neurological Sequelae from Neonatal HSV Disease

Virologically proven recurrences in the skin have been reported in up to 30% of survivors of neonatal HSV disease, but up to 10% of infants have a recurrent CNS infection that is associated with a worse outcome.[32,33] The efficacy of oral aciclovir suppressing long-term CNS recurrences and therefore neurological impairment has been evaluated in randomized controlled trials by the National Institute of Allergy and Infectious Diseases (NIAID) in the US.[35] The phase I/II trial of infants who received aciclovir 300 mg/m^2 per dose (≈10 mg/kg per dose) three times daily showed significant suppression of skin recurrences at 6 months; however, treatment was associated with significant risk of neutropenia. Results of the phase III trial evaluating the effect on CNS outcome from NIAID have yet to be reported.[36] A separate pilot open-label study of suppressive aciclovir therapy given for 2 years in 16 survivors of neonatal HSV infection showed suppression of neurological recurrences.[37]

Of concern are the reports of late CNS recurrences in two infants,[35,38] and isolation of an aciclovir-resistant mutant in another after receiving suppressive therapy for HSV in infancy.[35] At present, there is insufficient evidence to recommend routine suppressive oral antiviral therapy to prevent neurological sequelae from neonatal HSV disease.

5. Prevention of Vertical Transmission from Genital Herpes

5.1 Overview

Strategies to prevent neonatal HSV disease can be broadly subdivided into those that reduce exposure of the neonate to infectious virus at delivery, antenatal strategies to prevent seronegative women acquiring genital HSV infection for the first time in pregnancy, and postnatal interventions to prevent the development of disease in an infected infant. The following discussion is largely restricted to pharmacological interventions for the first two approaches.

5.2 Strategies to Limit Perinatal Exposure of the Fetus and Neonate to HSV

5.2.1 Antiviral Prophylaxis to Prevent Maternal Genital Herpes Recurrences

As the presence of virus in the genital tract is a major risk factor for vertical transmission of HSV, a number of groups have used oral antiviral drugs to reduce the risk of viral shedding in the birth canal at term so as to limit the newborn's exposure to the virus. To date, there have been no trials of intrapartum systemic antiviral therapy in women with recurrent genital herpes.

Antiviral agents with efficacy against HSV include the nucleoside analogues aciclovir, valaciclovir and famciclovir. Valaciclovir is the prodrug of aciclovir and is metabolized by the liver into the active form. Famciclovir is the oral prodrug of penciclovir, another nucleoside analogue that inhibits DNA synthesis. Aciclovir, valaciclovir and famciclovir have all been shown to be effective at reducing symptomatic recurrences of genital herpes and viral shedding in non-pregnant adults with genital herpes.[39-43] However, only aciclovir and valaciclovir have been used in pregnancy because of concerns about teratogenicity and carcinogenesis induced by famciclovir in animal studies. Animal studies of aciclovir in pregnancy have not demonstrated teratogenicity with its use at therapeutic concentrations, even with doses up to 30-fold higher than human doses, given to pregnant mice or in rabbits.[44] There is a large registry of the use of aciclovir and valaciclovir in pregnancy in the US, which has not shown evidence of human fetal teratogenicity or adverse outcomes of pregnancy.[45] However, the Aciclovir in Pregnancy Registry did not measure late-onset complications of pregnancy, including preterm delivery. Pharmacokinetic studies of aciclovir in pregnancy have shown similar plasma concentrations and drug clearance to non-pregnant women.[45,46] Aciclovir does appear to be concentrated in amniotic fluid but there has been no evidence of fetal drug accumulation.[45,46] Pharmacokinetic

studies of valaciclovir in pregnancy confirmed higher plasma aciclovir concentrations in pregnant women than in aciclovir therapy.[46,47] The effects of these agents on the fetus have not been evaluated in long-term follow-up studies after maternal use in pregnancy.

Table IV summarizes the study characteristics of trials of antiviral drugs in pregnancy.[47-56] Most studies have evaluated the efficacy of antiviral prophylaxis in women with a past medical history of genital herpes, as this group represents the largest population and are easy to identify, although they have a relatively low risk of transmitting virus to their infant. Only one randomized trial focused exclusively on prophylaxis for women who had experienced a laboratory-confirmed first episode of genital herpes in pregnancy, which is the group with the highest attack rate for vertical transmission.[54] A few studies of antiviral prophylaxis in pregnancy recruited women with either primary or recurrent herpes.[47,52] Outcomes measured in these trials included the presence of virus in the genital tract (by viral culture or more recently by PCR), the presence of active genital herpes at delivery, the rate of caesarean section and the incidence of neonatal herpes infection. Some studies also reported adverse effects from the agents in the mother and, in a few trials, in the newborn. Trials of aciclovir for preventing genital herpes recurrences in pregnancy have evaluated the efficacy of doses of 200 mg every 8 hours up to doses of 400 mg every 8 hours.[47-51,54-56] Two trials have evaluated the ability of valaciclovir to reduce genital herpes in pregnancy, both using dosages of 500 mg every 12 hours.[52,53] Most trials commenced antiviral therapy at 36 weeks' gestation.

To date, the efficacy of antiviral agents in preventing vertical transmission of HSV has been evaluated in two systematic reviews.[57,58] The first review was reported in 2003 by Sheffield et al.,[57] who analysed the use of aciclovir prophylaxis to prevent HSV recurrence at delivery. This review deemed five trials to be of sufficient quality for their analysis.[48-51,54] More recently, a systematic review has been reported by Hollier and Wendel in the Cochrane database.[58] This meta-analysis identified ten randomized trials of antiviral therapy, of which seven met the criteria of methodology and quality to be included in the final analysis. These were the same five aciclovir trials analysed by Sheffield et al. plus two additional trials of valaciclovir therapy.[52,53]

No trial was sufficiently powered to report the effectiveness of antiviral agents at reducing neonatal HSV infection, even when results were analysed by systematic methodology. However, meta-analysis did show that antiviral prophylaxis beginning at 36 weeks' gestation reduced the risk of clinical recurrence at the time of delivery by 10.7% (relative risk [RR] 0.28; 95% CI 0.18, 0.43).[58] Valaciclovir was as effective as aciclovir in reducing clinical and virological recurrences.[58] While rates of caesarean section for any indication did not differ between antiviral agent versus placebo or no treatment, caesarean section for clinical recurrence of genital herpes was reduced by 10% in the women who received antiviral prophylaxis (RR 0.3; 95% CI 0.2, 0.45) and the laboratory-confirmed detection of HSV at delivery was reduced by 5.8% (RR 0.14; 95% CI 0.05, 0.39).[58] Thus, antiviral prophylaxis does reduce both clinical and asymptomatic HSV virological recurrence at delivery and reduces clinical recurrence as an indication for caesarean section. These meta-analyses also appear to dispel the concern that antiviral therapy could suppress symptomatic recurrences after genital herpes in pregnancy and, thereby, may potentially increase neonatal exposure to HSV by converting clinically detectable lesions to asymptomatic recurrences (i.e. the woman is not offered a caesarean section because of symptomatic recurrence).

Potential harms to the mother from antiviral prophylaxis in pregnancy were reported in two trials.[48,53] Neither trial found evidence of nephrotoxicity from the antiviral agents. One trial reported on haematological toxicity and found no evidence that it was increased in the treatment group.[48] Reports of the effects of antiviral agents in pregnancy on the fetus and newborn are even more limited. Neonatal toxicity was only formally reported in the two recent valaciclovir studies.[52,53] These studies reported no

Table IV. Clinical trials of suppressive antiviral therapy for recurrent genital herpes simplex virus (HSV) in pregnancy

Study (year)	Oral dosage	Study design and no. enrolled[a]	Outcomes measured			
			genital clinical recurrence	virus detected in genital tract[b]	caesarean section for HSV	neonatal herpes
Recurrent genital HSV						
Stray-Pedersen[47] (1990)[c]	Aciclovir 200 mg qid	39 wk until delivery; not randomized 46 Aciclovir 46 No treatment	Y	Y	Y	N
Brocklehurst et al.[48] (1998)	Aciclovir 200 mg qid	36 wk until delivery; randomized 31 Aciclovir 32 Placebo	Y	N	Y	Y
Braig et al.[49] (2001)	Aciclovir 200 mg qid	36 wk until delivery; randomized 167 Aciclovir 121 Placebo 201 No treatment	N	Y	Y	Y
Scott et al.[50] (2002)	Aciclovir 400 mg q8 h	36 wk until delivery; randomized 116 Aciclovir 115 Placebo	Y	Y	Y	Y
Watts et al.[51] (2003)	Aciclovir 400 mg q8 h	36 wk until delivery; randomized 84 Aciclovir 78 Placebo	Y	Y	Y	Y
Sheffield et al.[52] (2006)[c]	Valaciclovir 500 mg q12 h	36 wk until delivery; randomized 170 Valaciclovir 168 Placebo	Y	Y	Y	Y
Andrews et al.[53] (2006)	Valaciclovir 500 mg q12 h	36 wk until delivery; randomized 57 Valaciclovir 55 Placebo	Y	Y	Y	Y
First-episode genital HSV[c,d]						
Scott et al.[54] (1996)	Aciclovir 400 mg q8 h	36 wk until delivery; randomized 21 Aciclovir 25 No treatment	Y	Y	Y	Y

a Includes clinical recurrence and prodrome.

b Includes swabs from vesicles and asymptomatic shedding.

c Trial includes women with primary genital HSV in pregnancy.

d First-episode patients. Serology not performed so could be primary or recurrent infection.

q*x*h = every *x* hours; **qid** = four times per day.

difference in fetal growth parameters, time of delivery, clinical status of the neonate at birth, or in haematological, biochemical, liver function or renal function tests at birth in offspring of the treatment group, and no clinical sequelae in the newborn at 1 month of delivery. Thus, while antiviral agents appear to reduce viral shedding and rates of caesarean section in pregnant women with genital herpes, there are still inadequate data regarding the long-term effects of these agents on the fetus and newborn.

Another consideration in the use of antiviral agents to prevent genital herpes recurrences in pregnancy is cost. A review by Brown[59] evaluated economic analyses of prophylactic antivirals in pregnancy and concluded that suppressive aciclovir from 36 weeks' gestation decreases antenatal costs by reducing costs associated with caesarean section, with the greatest benefit being gained in women with first-episode herpes or frequent recurrences, with six or more reactivations per year.

Many experts would use maternal antiviral prophylaxis for confirmed primary genital HSV infection in late pregnancy.[59] However, the use of antiviral prophylaxis for suppression of shedding from recurrent genital herpes in pregnant women remains controversial, and should be considered only after careful analysis of the benefits and potential harms to the mother and fetus.

5.2.2 Diagnosis of the Type of Maternal Genital HSV Infection and Non-Pharmacological Strategies to Reduce Perinatal Exposure to HSV

A woman who presents with an initial episode of genital HSV infection in pregnancy should have type-specific serology and viral culture/PCR of the genital lesion in order to determine whether she has primary or recurrent infection. This is necessary in order to advise appropriately on the use of prophylactic therapy, to counsel about the risk of neonatal infection, and to set up an appropriate management plan for labour and delivery.

Non-pharmacological ways to reduce perinatal exposure to HSV include limiting the use of invasive procedures in women with a history of genital herpes or known primary disease in pregnancy and performing caesarean delivery for women with herpetic lesions in the genital tract at the onset of labour. Invasive procedures such as use of scalp electrodes and instruments to assist vaginal deliveries provide a portal of entry for the virus through the newborn mucosa and are associated with an increased risk of neonatal infection.[8] A prospective observational study by Brown and colleagues[8] has shown that caesarean delivery reduces the risk of transmission of HSV to the neonates when virus is present in the genital tract, although it is not completely protective. For women with primary disease who have not seroconverted or women with previous genital HSV infection and active disease in labour, caesarean section is recommended provided there has not been prolonged rupture of membranes.[60] Serial antenatal genital viral cultures of women with a history of genital HSV disease are not predictive of the presence of virus at delivery and should not be performed.[61]

5.3 Strategies to Reduce Maternal Genital HSV Infection in Pregnancy

The major risk factor for vertical transmission of herpes is primary genital infection. Therefore, attempts at preventing neonatal HSV disease have also been directed towards preventing maternal genital HSV infection before or during pregnancy. Such approaches include the following: (i) antenatal counselling of women about ways to reduce exposure to HSV, with or without serological testing of women and their partners for type-specific HSV antibodies; (ii) the use of suppressive aciclovir in the partner with a history of recurrent genital (or oral) herpes; (iii) behavioural strategies such as the avoidance of oral-genital or genital-genital contact, especially near term; (iv) use of condoms in partners; and (v) vaccines against genital herpes. The use of topical microbicide creams or immunoadjuvants such as Toll-like receptor ligands[62,63] to reduce genital HSV infection have not been evaluated for safety and efficacy in pregnant women or their partners.

5.3.1 Screening and Counselling

The risk to HSV seronegative women for acquiring genital herpes can be from oral-genital contact or genital-genital contact. The performance of routine antenatal HSV serology and its role in antenatal counselling is controversial. The reader is referred elsewhere for detailed consideration of arguments for and against this practice.[63-66] It is generally not recommended in countries with low HSV-2 seroprevalence and/or where the incidence of neonatal HSV disease is very low.[67] Screening of high-risk women, such as those with partners with a history of oral or genital herpes, is an alternative approach. However, the high frequency of asymptomatic genital herpes means that the absence of a history of genital herpes in a women or her partner does not always exclude a previous infection.

If screening is to be performed, both HSV serotypes should be measured in the woman and her partner. However, the detection of HSV-1 antibodies does not distinguish between the presence of oral or genital infection. Some experts advise that antenatal serological screening for HSV-2 is cost effective[68] and can allow the targeted use of interventions to prevent transmission.[69] An alternative approach is to counsel all pregnant women and their partners about methods to prevent maternal acquisition of HSV during pregnancy, such as the avoidance of oral-genital contact, abstaining from genital intercourse in the third trimester and the use of condoms by the partner.[59] While these approaches have been shown to reduce transmission in small studies of serodiscordant couples,[59] their uptake in the general population is not always high.

5.3.2 Antiviral Suppressive Therapy in a Serodiscordant Partner

Another potential approach to reducing the acquisition of maternal genital HSV infection in pregnancy is the use of suppressive antiviral therapy in a partner with a history of genital herpes or with documented HSV-2 seropositivity. Valaciclovir, aciclovir and famciclovir have all been shown to reduce reactivation and shedding from genital herpes.[42,43] Oral valaciclovir 500 mg every 12 hours has been specifically shown to reduce transmission of HSV to non-pregnant susceptible partners in serodiscordant couples.[41] The efficacy of this approach has yet to be evaluated in the context of a seronegative pregnant partner. A recent study from the US[68] reported that HSV-2 serological testing of pregnant women and their partners, coupled with suppressive therapy for seropositive women and for seropositive partners of seronegative pregnant women, might be a cost-effective way to prevent neonatal HSV disease compared with no screening. The cost benefit may not extend to regions where the seroprevalence of HSV-2 and/or the incidence of neonatal HSV disease is not as high.

5.3.3 Vaccines Against (Maternal) Genital HSV Disease

Another way to prevent maternal acquisition of HSV would be by prophylactic vaccination against HSV of seronegative women. The aim of a prophylactic vaccine against genital HSV would be to limit viral replication at the site of infection and reduce the burden of latency in the ganglia, thereby preventing or reducing the frequency of clinical or asymptomatic shedding.[70] The biological properties of the virus, such as the ability to hide from the immune response in the sensory ganglia and to modulate the immune response,[2,3,71] make this a difficult task.

Not surprisingly, there has been a long history of failed attempts to develop a vaccine against genital herpes. To date, the only vaccine that has shown partial success in a phase III clinical trial is an HSV-2 glycoprotein D vaccine with adjuvant MPL-alum.[72] This vaccine was trialled in HSV serodiscordant couples and was shown to prevent disease significantly but not infection in women who were seronegative for both HSV-1 and HSV-2. It showed no protection in HSV-1 seronegative men and did not improve protection already afforded by pre-existing immunity to HSV-1 in women. This vaccine is currently being evaluated in adolescent girls prior to the onset of sexual activity and HSV-1 acquisition. Randomization has recently been completed but data analysis is yet to be performed.[73] It remains to be seen if such a vaccine will affect vertical transmission of genital herpes, particularly in countries

where neonatal HSV disease is predominantly caused by HSV-1.

5.4 Postnatal Interventions to Prevent Neonatal Herpes

Theoretically, interventions could be given to newborn infants exposed perinatally to HSV to prevent infection or disease. Such strategies include the use of systemic aciclovir in exposed infants, recombinant HSV-specific neutralizing antibody and immunostimulants. There are currently no data available on the efficacy of neonatal antiviral therapy after exposure to HSV at delivery, although many clinicians would advocate its use in high risk settings (e.g. those born to mothers with confirmed primary genital HSV disease).[74]

6. Conclusions

Neonatal herpes, although uncommon, is a devastating disease. Antiviral agents given in late pregnancy have been shown to reduce genital HSV shedding and the rate of caesarean delivery. However, these trials are inadequately powered to determine the effect of therapy on the incidence of neonatal HSV disease. Future research should be directed towards investigating the role of intrapartum antiviral agents to prevent transmission, developing rapid tests to determine serostatus and viral shedding at delivery, developing postnatal strategies to limit neonatal disease and towards developing a vaccine against genital herpes with enhanced immunogenicity.

Acknowledgements

No sources of funding were used in the preparation of this article. The author has no conflicts of interest that are directly relevant to the content of this review.

References

1. Whitley R. Herpes simplex viruses. In: Knipe DM, Howle PM, editors. Fields virology. 5th ed. Philadelphia (PA): Lippincott Williams & Wilkins, 2007: 2502-76
2. Hill A, Jugovic J, York I, et al. Herpes simplex virus turns off the TAP to evade host immunity. Nature 1995; 375: 411-5
3. Lilley BN, Ploegh HL. Viral modulation of antigen presentation: manipulation of cellular targets in the ER and beyond. Immunol Rev 2005; 207: 126-44
4. Chen KT, Segu M, Lumey LH, et al., on behalf of New York City Perinatal AIDS Collaborative Transmission Study (PACTS) Group. Genital herpes simplex virus infection and perinatal transmission of human immunodeficiency virus. Obstet Gynecol 2005; 106: 1341-8
5. Ozouaki F, Ndjoyi-Mbiguino A, Legoff J, et al. Genital shedding of herpes simplex virus type 2 in childbearing-aged and pregnant women living in Gabon. Int J STD AIDS 2006; 17: 124-7
6. Kimberlin DW. Neonatal herpes simplex infection. Clin Microbiol Rev 2004; 17: 1-13
7. Brown ZA, Benedetti J, Ashley R, et al. Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labor. N Engl J Med 1991; 324: 1247-52
8. Brown ZA, Wald A, Morrow RA, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA 2003; 289: 203-9
9. Malkin JE. Epidemiology of genital herpes simplex virus infection in developed countries. Herpes 2004; 11 Suppl. 1: 2-23A
10. Tookey P, Peckham CS. Neonatal herpes simplex virus infection in the British Isles. Paediatr Perinat Epidemiol 1996; 10: 432-42
11. Freedman E, Mindel A, Jones CA. Epidemiological and laboratory aids for the diagnosis of neonatal herpes: an Australian perspective. Herpes 2004; 11: 38-44
12. Nahmias AJ. Neonatal HSV infection. Part II: obstetric considerations – a tale of hospitals in two cities (Seattle and Atlanta, USA). Herpes 2004; 11: 41-4
13. Whitley RJ. Neonatal herpes simplex virus infections. Clin Perinatol 1988; 15: 903-16
14. Whitley R, Arvin A, Prober C, et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. N Engl J Med 1991; 324: 450-4
15. Baldwin S, Whitley RJ. Intrauterine herpes simplex virus infection. Teratology 1989; 39: 1-10
16. Kimberlin DW, Lin CY, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Pediatrics 2001; 108: 223-9
17. Whitley R, Arvin A, Prober C, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. Infectious Diseases Collaborative Antiviral Study Group. N Engl J Med 1991; 324: 444-9
18. Brown ZA, Vontver LA, Benedetti J, et al. Effects on infants of a first episode of genital herpes during pregnancy. N Engl J Med 1987 Nov 12; 317 (20): 1246-51
19. Brown EL, Gardella C, Malm G, et al. Effect of maternal herpes simplex virus (HSV) serostatus and HSV type on risk of neonatal herpes. Acta Obstet Gynecol Scand 2007; 86: 523-9

20. Kulhanjian JA, Soroush V, Au DS, et al. Identification of women at unsuspected risk of primary infection with herpes simplex virus type 2 during pregnancy. N Engl J Med 1992; 326: 916-20
21. Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during pregnancy. N Engl J Med 1997; 337: 509-15
22. Yeager AS, Arvin AM, Urbani LJ, et al. Relationship of antibody to outcome in neonatal herpes simplex virus infections. Infect Immun 1980; 29: 532-8
23. Bollen L, Whitehead S, Mock P, et al. Maternal herpes simplex virus type 2 coinfection increases the risk of perinatal HIV transmission: possibility to further decrease transmission? AIDS 2008; 22: 1169-76
24. Corey L. Herpes simplex virus type 2 and HIV-1: the dialogue between the 2 organisms continues. J Infect Dis 2007; 195: 1242-4
25. Chen KT, Tuomala RE, Chu C, et al. No association between antepartum serologic and genital tract evidence of herpes simplex virus-2 coinfection and perinatal HIV-1 transmission. Am J Obstet Gynecol 2008; 198: 399.e1-5
26. Diamond C, Mohan K, Hobson A, et al. Viremia in neonatal herpes simplex virus infections. Pediatr Infect Dis J 1999; 18: 487-9
27. Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret's. Herpes 2004; 11 Suppl. 2: 57-64A
28. Koskiniemi M, Happonen JM, Järvenpää AL, et al. Neonatal herpes simplex virus infection: a report of 43 patients. Pediatr Infect Dis J 1989; 8: 30-5
29. Kimberlin D. Herpes simplex virus, meningitis and encephalitis in neonates. Herpes 2004; 11 Suppl. 2: 65-76A
30. Kimura H, Futamura M, Kito H, et al. Detection of viral DNA in neonatal herpes simplex virus infections: frequent and prolonged presence in serum and cerebrospinal fluid. J Infect Dis 1991; 164: 289-93
31. Domingues RB, Lakeman FD, Mayo MS, et al. Application of competitive PCR to cerebrospinal fluid samples from patients with herpes simplex encephalitis. J Clin Microbiol 1998; 36: 2229-34
32. Kimberlin DW, Lin CY, Jacobs RF, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. Pediatrics 2001; 108: 230-8
33. Whitley RJ, Nahmias AJ, Soong SJ, et al. Vidarabine therapy of neonatal herpes simplex virus infection. Pediatrics 1980; 66: 495-501
34. Levin MJ, Weinberg A, Leary JJ, et al. Development of acyclovir-resistant herpes simplex virus early during the treatment of herpes neonatorum. Pediatr Infect Dis J 2001 Nov; 20 (11): 1094-7
35. Kimberlin D, Powell D, Gruber W, et al. Administration of oral acyclovir suppressive therapy after neonatal herpes simplex virus disease limited to the skin, eyes and mouth: results of a phase I/II trial. Pediatr Infect Dis J 1996; 15: 247-54
36. National Center for Research Resources (NCRR) and the National Institute of Allergy and Infectious Diseases (NIAID). Phase III randomized, placebo-controlled study of acyclovir oral suspension for neonatal herpes simplex virus infection limited to the skin, eyes, and mouth [Clinical Trials.gov identifier NCT00004757]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2009 Feb 23]
37. Tiffany KF, Benjamin Jr DK, Palasanthiran P, et al. Improved neurodevelopmental outcomes following long-term high-dose oral acyclovir therapy in infants with central nervous system and disseminated herpes simplex disease. J Perinatol 2005; 25: 156-61
38. Fonseca-Aten M, Messina AF, Jafri HS, et al. Herpes simplex virus encephalitis during suppressive therapy with acyclovir in a premature infant. Pediatrics 2005; 115: 804-9
39. Wald A, Zeh J, Barnum G, et al. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. Ann Intern Med 1996; 124 (1 Pt 1): 8-15
40. Wald A, Corey L, Cone R, et al. Frequent genital herpes simplex virus 2 shedding in immunocompetent women: effect of acyclovir treatment. J Clin Invest 1997; 99: 1092-7
41. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med 2004; 350: 11-20
42. Gupta R, Wald A, Krantz E, et al. Valacyclovir and acyclovir for suppression of shedding of herpes simplex virus in the genital tract. J Infect Dis 2004; 190: 1374-81
43. Leone P, Warren T, Hamed K, et al. Famciclovir reduces viral mucosal shedding in HSV-seropositive persons. Sex Transm Dis 2007; 34: 900-7
44. Scott LL. Prevention of perinatal herpes: prophylactic antiviral therapy? Clin Obstet Gynecol 1999; 42: 134-48
45. Tyring SK, Baker D, Snowden W. Valacyclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years' experience with acyclovir. J Infect Dis 2002; 186 Suppl. 1: S40-6
46. Kimberlin DF, Weller S, Whitley RJ, et al. Pharmacokinetics of oral valacyclovir and acyclovir in late pregnancy. Am J Obstet Gynecol 1998; 179: 846-51
47. Stray-Pedersen B. Acyclovir in late pregnancy to prevent neonatal herpes simplex [letter]. Lancet 1990; 336 (8717): 756
48. Brocklehurst P, Kinghorn G, Carney O, et al. A randomised placebo controlled trial of suppressive acyclovir in late pregnancy in women with recurrent genital herpes infection. Br J Obstet Gynaecol 1998; 105: 275-80
49. Braig S, Luton D, Sibony O, et al. Acyclovir prophylaxis in late pregnancy prevents recurrent genital herpes and viral shedding. Eur J Obstet Gynecol Reprod Biol 2001; 96: 55-8
50. Scott LL, Hollier LM, McIntire D, et al. Acyclovir suppression to prevent recurrent genital herpes at delivery. Infect Dis Obstet Gynecol 2002; 10: 71-7
51. Watts DH, Brown ZA, Money D, et al. A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and cesarean delivery. Am J Obstet Gynecol 2003; 188: 836-43
52. Sheffield JS, Hill JB, Hollier LM, et al. Valacyclovir prophylaxis to prevent recurrent herpes at delivery: a randomized clinical trial. Obstet Gynecol 2006; 108: 141-7
53. Andrews W, Kimberlin D, Whitley R, et al. Valacycovir therapy to reduce recurrent genital herpes in pregnant women. Am J Obstet Gynecol 2006; 194: 774-81

54. Scott LL, Sanchez PJ, Jackson GL, et al. Acyclovir suppression to prevent cesarean delivery after first-episode genital herpes. Obstet Gynecol 1996; 87: 69-73
55. Scott LL, Hollier LM, Jackson G, et al. Acyclovir suppression to prevent cesarean delivery after first episode genital simplex infection [abstract]. Am J Obstet Gynecol 1998; 178 (1 Pt 2): 12
56. Scott LL, Hollier LM, Baum A, et al. Prevention of recurrent genital herpes at delivery using acyclovir suppression for herpes infection diagnosed prior to pregnancy-an interim analysis. Am J Obstet Gynecol 1998; 178 (1 Pt 2): S213
57. Sheffield JS, Hollier LM, Hill JB, et al. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. Obstet Gynecol 2003; 102 (6): 1396-403
58. Hollier LM, Wendel GD. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection. Cochrane Database Syst Rev 2008; (1): CD004946
59. Brown Z. Preventing herpes simplex virus transmission to the neonate. Herpes 2004; 11 Suppl. 3: 175-86A
60. ACOG Committee on Practice Bulletins-Gynecology. ACOG practice bulletin no. 8 Oct 1999. Management of herpes in pregnancy: clinical management guidelines for obstetrician-gynecologists. Int J Gynaecol Obstet 2000 Feb; 68 (2): 165-73
61. Garland SM, Lee TN, Sacks S. Do antepartum herpes simplex virus cultures predict intrapartum shedding for pregnant women with recurrent disease? Infect Dis Obstet Gynecol 1999; 7: 230-6
62. Guzman EM, Cheshenko N, Shende V, et al. Amphipathic DNA polymers are candidate vaginal microbicides and block herpes simplex virus binding, entry and viral gene expression. Antivir Ther 2007; 12: 1147-56
63. Gill N, Davies EJ, Ashkar AA. The role of toll-like receptor ligands/agonists in protection against genital HSV-2 infection. Am J Reprod Immunol 2008; 59: 35-43
64. Arvin AM. The argument against: should all pregnant women be offered type-specific serological screening for HSV infection? [debate]. Herpes 2002; 9: 48-50
65. Wilkinson D, Barton S, Cowan F. HSV-2 specific serology should not be offered routinely to antenatal patients. Rev Med Virol 2000; 10 (3): 145-53
66. Brown ZA. HSV-2 specific serology should be offered routinely to antenatal patients. Rev Med Virol 2000; 10: 141-4
67. Copas AJ, Cowan FM, Cunningham AL, et al. An evidence based approach to testing for antibody to herpes simplex virus type 2. Sex Transm Infect 2002; 78: 430-4
68. Baker D, Brown Z, Hollier LM, et al. Cost-effectiveness of herpes simplex virus type 2 serologic testing and antiviral therapy in pregnancy. Am J Obstet Gynecol 2004; 191: 2074-84
69. Lafferty WE. The changing epidemiology of HSV-1 and HSV-2 and implications for serological testing. Herpes 2002; 9: 51-5
70. Stanberry LR, Cunningham AL, Mindel A, et al. Prospects for control of herpes simplex virus disease through immunization. Clin Infect Dis 2000; 30: 549-66
71. Koelle DM, Corey L. Herpes simplex: insights on pathogenesis and possible vaccines. Annu Rev Med 2008; 59: 381-95
72. Stanberry LR, Spruance SL, Cunningham AL, et al. Glycoprotein-D-adjuvant vaccine to prevent genital herpes. N Engl J Med 2002; 347: 1652-61
73. GlaxoSmithKline. A double-blind, randomized, controlled study to evaluate the immunogenicity and safety of a GlaxoSmithKline Biologicals' investigational vaccine regimen in healthy female subjects aged 10-17 years [online]. Available from URL: http://www.gskclinicalstudyregister.com/files/pdf/20344.pdf [Accessed 2009 Feb 23]
74. Jones CA, Isaacs D. Management of herpes simplex virus infections in childhood. Curr Paediatr 2004; 14: 131-6

Correspondence: Assoc. Prof. *Cheryl A. Jones*, Centre for Perinatal Infection Research, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia.
E-mail: cherylj@chw.edu.au