Recommendations from the
IHMF Management Strategies Workshop and
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HERPESVIRUS INFECTIONS IN PREGNANCY

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management strategies in herpes

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Introduction

The *International Herpes Management Forum* (IHMF) was established to improve the awareness, understanding, counselling and management of infections caused by herpesviruses. Steered by Professor Richard Whitley, Dr Martin Wood, Professor Lawrence Corey, Professor Paul Griffiths and Dr Jean-Elie Malkin, the IHMF involves international opinion leaders in all aspects of the management of herpesvirus infections.

A *Management Strategies Workshop* was held on 23–24 June 1999 to discuss the management of herpes simplex virus, cytomegalovirus and varicella zoster virus infections in pregnancy. The Workshop objectives were to develop strategies to improve the care of both mother and child. To achieve this, recommendations have been developed to diagnose and manage the pregnant woman with herpesvirus infections and the neonate exposed to them.

The draft recommendations were discussed at the *7th Annual Meeting of the IHMF* on 3–5 December 1999. The Annual Meeting provided a forum for debate, amendment and ratification of these guidelines.

Structure of this *Management Strategies* Publication

The natural history of herpesvirus infections is important in the context of neonatal disease. In general, the risk of neonatal sequelae following maternal infection with herpes simplex virus, varicella zoster virus or cytomegalovirus is greater in following primary infection compared with recurrent infection. However, other factors also influence the likelihood of complications. Therefore, an understanding of the epidemiology of individual infections, together with a consideration of the factors that influence acquisition of infection by the fetus or neonate and the outcome of infection can help in their management. The epidemiology and natural history of each infection is followed by sections on management. Where the management approaches to the pregnant woman and neonate are distinct, separate chapters are devoted to each patient group.

Contents

Herpes Simplex Virus Infection in Pregnant Women and Neonates

Pre-Natal Management of Herpes Simplex Virus Infection

1A. First episode genital herpes during pregnancy

- Disseminated or presumed maternal primary herpes simplex virus (HSV) infection should be treated with aciclovir (*Category 2 recommendation*)*
- For a woman presenting with a first episode of genital herpes in the third trimester, every effort should be made to characterize it serologically (e.g. primary versus non-primary)
- In women with a primary HSV infection after 34 weeks, delivery by elective Caesarean section should be considered (*Category 2 recommendation*).

1B. Recurrent maternal herpes during pregnancy

- Aciclovir prophylaxis in late pregnancy for women with known recurrences of genital herpes is not currently recommended (*Category 2 recommendation*)
- The recommendation not to provide aciclovir prophylaxis in late pregnancy for women with known recurrences should be reviewed as results become available (*Research need recommendation*).

1C. Pre-natal type-specific serological testing for maternal herpes simplex virus infection

- Type-specific serological testing for HSV types 1 and 2 may have value in the management of the pregnant woman and her partner. Depending on local epidemiology and test performance, it has the potential to identify:
  – previously infected individuals
  – those who seroconvert, if serial samples are taken
  – discordant couples, if partners are screened
- Type-specific serological testing alone will not differentiate genital HSV-1 infection and orolabial HSV-1 infection.

Management of Herpes Simplex Virus Infection at Delivery

2A. Mode of delivery indications for Caesarean section

- In the past, Caesarean section has been used widely. Caesarean section and other management options should be discussed with the patient (*Category 3 recommendation*)
- Controlled trials of management policies to reduce the use of Caesarean section are required (*Research need recommendation*)
- Mode of delivery may be based on clinical findings at the time of delivery (*Category 2 recommendation*). The presence of obvious herpetic lesions is only a relative indication for Caesarean section.

2B. Avoidance of invasive monitoring

- Invasive monitoring of the neonate should only be used for defined obstetrical indications (*Category 3 recommendation*).

* Please refer to Appendix (page 88) for an explanation of the Recommendation Categories

Management of the Neonate with Possible Herpes Simplex Virus Infection

3A. Diagnosis of suspected or proven herpes simplex virus in the neonate

- The high risk of death or neurological damage with delayed or no treatment of neonatal HSV infection requires that diagnosis be pursued promptly whenever the infection is suspected and that empiric treatment with intravenous aciclovir be initiated at the time diagnostic tests are ordered
- Neonatal herpes may occur in the absence of skin lesions. Thus, diagnostic methods are required
- Whenever neonatal HSV infection is suspected, material from skin or mucosal lesions, conjunctival swabs, mouth swabs, rectal swabs, urine and cerebrospinal fluid (CSF) should be submitted to the laboratory for virus culture and/or polymerase chain reaction (PCR) detection of HSV (*Category 1 recommendation*)
- Evidence of disseminated or central nervous system (CNS) infection should be sought by performing liver function tests, complete blood cell count (CBC), CSF analysis and, if there are any respiratory abnormalities, a chest X-ray (*Category 1 recommendation*)
- PCR analysis of the CSF for HSV DNA should be used to diagnose suspected neonatal herpes (*Category 2 recommendation*).

3B. Treatment of neonatal herpes simplex virus infection

- Intravenous aciclovir (20 mg/kg every 8 hours) is recommended for neonatal HSV infection (*Category 2 recommendation*). Early therapy, which may improve long-term neurological outcome, is recommended (*Category 1 recommendation*)
- The duration of intravenous aciclovir (20 mg/kg every 8 hours) treatment should be 14 days for disease that is limited to the skin, eyes or mouth (i.e. normal CSF), and 21 days for other forms of neonatal HSV infection (i.e. abnormal CSF), (*Category 1/2 recommendation*). This recommendation applies to each of the clinical scenarios below
- In no circumstances should oral or topical therapy be used to treat neonatal HSV infection (*Category 1 recommendation*)
- The value of suppressive antiviral therapy for prevention of recurrences after the initial treatment of neonatal HSV infection has not been established (*Category 2 recommendation*).

Clinical Scenario 1: Infant born to a mother with clinically apparent first episode genital herpes at delivery

- Ideally, the infant should be examined by a paediatrician experienced at identifying the signs of neonatal herpes
- Specimens for virological assays (e.g. culture, PCR) should be obtained from the infant at delivery. (Follow recommendations for diagnosis in 3A)
- Prophylactic intravenous aciclovir therapy at 60 mg/kg/day in three divided doses for 14 days is recommended (*Category 2 recommendation*)
- If clinical signs compatible with HSV infection develop, a work-up of the central nervous system is indicated, including CSF examination by PCR
- If evidence of disseminated or CNS disease (i.e. abnormal CSF), the infant should be treated with intravenous aciclovir therapy (60 mg/kg/day in three divided doses) for 21 days.

Clinical scenario 2: Infant born to a mother with clinically apparent recurrent genital herpes at delivery

- Ideally, the infant should be examined by a paediatrician experienced at identifying the signs of neonatal herpes

- If lesions are present on the infant, collect specimens for routine culture
- The parents should be educated about the disease
- If the infant develops clinical signs compatible with neonatal HSV infection, collect specimens, including CSF, for virological assays (follow the detailed recommendations for diagnosis in 3A)
- The treatment with intravenous aciclovir (60 mg/kg/day in three divided doses for 14–21 days) started immediately (at the time diagnostic tests are ordered) pending results of the laboratory analysis and clarification of the clinical course
- If evidence of disseminated or CNS disease (i.e. abnormal CSF), the longer treatment period should be utilized (*Category 2 recommendation*)
- If a CSF analysis is not available, the longer treatment period should be used.

Clinical scenario 3: Infant born to mother with a history of genital herpes but no obvious lesions at delivery

- Ideally, the infant should be examined by a paediatrician experienced at identifying the signs of neonatal herpes
- In this setting parents should be educated about the signs of disease
- If any clinical signs compatible with neonatal herpes develop, specimens, including CSF, for virological assays should be obtained (follow the detailed recommendations for diagnosis in 3A)
- The treatment with intravenous aciclovir (60 mg/kg/day in three divided doses for 14–21 days) started immediately (at the time diagnostic tests are ordered) pending results of the laboratory analysis and clarification of the clinical course
- If evidence of disseminated or CNS disease (i.e. abnormal CSF), the longer treatment period should be utilized
- If a CSF analysis is not available, the longer treatment period should be used.

Clinical scenario 4: Infant with clinical presentation compatible with neonatal herpes simplex virus infection

- Specimens for virological assays (e.g. culture, PCR) should be obtained from the infant at delivery. (Follow recommendations for diagnosis in 3A)
- A work-up of the CNS is indicated, including CSF examination by PCR
- The treatment with intravenous aciclovir (60 mg/kg/day in three divided doses for 14–21 days) started immediately (at the time diagnostic tests are ordered) pending results of the laboratory analysis and clarification of the clinical course
- If evidence of disseminated or CNS disease (i.e. abnormal CSF), the infant should be treated with intravenous aciclovir therapy (60 mg/kg/day in three divided doses) for 21 days.

3C. Monitoring treatment of neonatal herpes simplex virus infection

- Infants in whom there is persistence of HSV DNA in the CSF following completion of antiviral therapy are more likely to die or suffer serious neurological impairment than infants whose post-therapy CSF specimens are PCR negative (*Category 3 recommendation*)
- Quantitative PCR testing of serial CSF samples may also help monitor progress and be useful as a prognostic tool (*Research need recommendation*).

3D. Potential diagnostic methods

- PCR of peripheral blood mononuclear cells and plasma may also be a useful diagnostic tool (*Research need recommendation*)

- PCR to detect HSV DNA in dried blood spots on Guthrie cards may be useful for retrospective detection of HSV infection (*Research need recommendation*).

Neonatal Herpes Simplex Virus Infection – Priorities for Research

- It is important to evaluate prospectively:
  – PCR detection of HSV DNA in the CSF and blood
  – family counselling
  – suppressive antiviral therapy (controlled trials are in progress)
- A vaccine to prevent neonatal herpes is desirable.

Cytomegalovirus Infection in Pregnant Women and Neonates

Natural History in Pregnancy

- Primary maternal cytomegalovirus (CMV) infection represents more of a risk to the fetus than recurrent maternal infection
- Primary and recurrent CMV infections in the mother are usually asymptomatic (*Category 1 recommendation*)
- Laboratory assays can reliably confirm primary infection but are not yet widely available
- No assays exist to detect recurrent infection in the mother that may be transmitted to the fetus.

Pre-Natal Screening and Diagnosis

- Routine serological screening of pregnant women for CMV infection cannot be recommended as a standard of care at the present time. If antiviral therapy that can safely prevent or treat fetal infection is developed, then the role of maternal pre-natal screening must be reassessed. Screening some high-risk women or populations may be of value now, although choices for intervention are limited (*Research need recommendation*)
- Fetal CMV infection can be diagnosed accurately by detection of virus in amniotic fluid by culture or PCR
- Routine screening for CMV infection during pregnancy is not indicated at present. This should be reviewed if a therapeutic intervention of proven value becomes available (*Research need recommendation*).

Screening for and Diagnosis of Congenital Cytomegalovirus Infection

- The diagnosis of congenital CMV infection should be made by the detection of virus in body fluids during the first 3 weeks of life. Urine or saliva are recommended
- As over 90% of newborns with congenital CMV infection are asymptomatic at birth, they will not be diagnosed unless newborns are screened. Screening for congenital CMV infection can be accomplished accurately by testing saliva or urine for virus. Universal screening cannot be recommended until data supporting cost-effectiveness are available
- Isolation of CMV from urine or saliva is the gold standard for diagnosis or screening. PCR detection should work well for diagnosis, but has not been adequately evaluated for screening purposes.

Treatment and Prevention of Congenital Cytomegalovirus Infection

- Currently, no antiviral treatment for congenital CMV infection has been shown to decrease the frequency or severity of CNS damage in controlled clinical trials
- It is possible that the use of ganciclovir in some newborns with cytomegalic inclusion disease could decrease mortality or severe morbidity in the newborn period, although this has not been demonstrated in controlled clinical trials. Compassionate use of ganciclovir in newborns with life-threatening or vision-threatening congenital CMV infection is probably justified
- There is currently no method of proven efficacy for preventing maternal CMV infection during pregnancy.

Follow-Up

- Infants and children with congenital CMV infection should have audiological evaluations at least twice a year for the first 3 years of life and annually up to school age because of the risk of progressive and late onset hearing loss
- Every infant with congenital CMV infection should have at least one fundoscopic examination for retinal lesions. If lesions are present, the follow-up examinations are recommended at least annually
- Infants and children with congenital CMV infection should receive services aimed at maximizing their hearing, speech, vision, cognitive and motor functions if any impairments are found.

Research Initiatives

- Development of a vaccine to prevent maternal and congenital CMV infection
- Development of antiviral therapy which can be used safely in pregnant women with primary CMV infection to prevent transmission of virus to the fetus
- Development of antiviral therapy which can be used pre-natally to treat the infected fetus
- Development of antiviral therapy which can be used safely in newborns and infants with congenital CMV infection to decrease the frequency and severity of impairments of hearing, vision, cognitive and motor functions.

Varicella Zoster Virus Infection in Pregnant Women and Neonates

Diagnosis:Pregnant Woman

- A history of previous varicella zoster virus (VZV) infection is generally accepted as proof of immunity. But, when it can be done in a timely fashion, determination of immune status by ELISA is advisable before administration of varicella zoster immune globulin (VZIG)
- VZV infection is generally suspected from clinical presentation, although laboratory testing may be required for confirmation
- The presence of immunoglobulin (Ig) G antibody in serum in the absence of symptoms indicates previous infection. The detection of IgM with a rising IgG titre in maternal serum indicates a recent infection

- Serological testing is indicated when immunity to varicella must be determined, for example, when a past history is unreliable.

Pre-Natal Diagnosis

- As the risk of congenital varicella syndrome is low (1–2%), the risk associated with the invasive pre-natal diagnostic methods (amniocentesis or cordocentesis) suggests that they are unlikely to be widely used diagnostic tools for congenital varicella syndrome
- Pre-natal diagnosis of congenital varicella syndrome following maternal primary VZV infection may allow the woman to make an informed choice about termination of pregnancy
- Ultrasound screening between 19 and 23/24 weeks of gestation is recommended for all women who have varicella in the first 21 weeks of pregnancy. If the sonographic findings are abnormal, fetal blood and amniotic fluid obtained in weeks 22 to 23 of gestation should be tested for VZV DNA. Testing for VZV-specific IgM in fetal blood is not helpful (*Category 2 recommendation*).

Diagnosis in the Newborn

- The diagnosis of varicella infection in the newborn is usually based on clinical findings. The clinical course of varicella in newborns can vary in progression and severity.

Pre-Exposure Prophylaxis:Vaccination

- Vaccination of VZV seronegative women of child-bearing age who are currently not pregnant should be considered (*Category 3 recommendation*).

Post-Exposure Prophylaxis in the Pregnant Woman

- VZIG should be administered as soon as possible to the seronegative mother following exposure to VZV in the first 20 weeks of gestation. VZIG may be administered to the susceptible woman who is exposed to VZV in the third trimester to reduce the risk of varicella (*Category 2 recommendation*)
- The value of post-exposure aciclovir prophylaxis for the susceptible pregnant woman should be assessed in clinical trials (*Research need recommendation*).

Pregnant Woman with Varicella

- The complications of varicella are more common in adults. Given the limited Registry data available, there is no apparent reason to withhold aciclovir at any time in pregnancy (*Category 2 recommendation*). The dosage and route of administration is determined by the severity of disease. The woman should be advised about the use of a drug unlicensed in pregnancy
- More data are required on long-term follow-up of children exposed to aciclovir *in utero* (*Research need recommendation*)
- If a woman has severe or complicated disease (e.g. pneumonitis), intravenous aciclovir should be given (10 mg/kg every 8 hours for 7 days or longer), (*Category 3 recommendation*)
- Pregnant women with less severe disease should be treated with oral aciclovir (800 mg five times daily for 7 days), (*Category 3 recommendation*)
- The pregnant woman with varicella should avoid contact with all other pregnant women and neonates until her lesions have crusted.

Post-Exposure Prophylaxis in the Neonate

- Administration of VZIG to the infant is advised if the mother develops varicella 7 days before or after delivery
- The neonate of a mother with active varicella should be isolated while in hospital, from birth to day 21 (or day 28 if the infant has been given VZIG), whereas neonates with congenital varicella syndrome do not need isolation from other children.

Treatment of the Neonate

- Neonates exposed to VZV should be observed closely. If they develop vesicles, they should be treated early with intravenous aciclovir
- Occasionally, neonates may develop varicella despite receiving VZIG. This is usually mild, but therapy with aciclovir should be considered.

Herpes Zoster in the Pregnant Woman

- Herpes zoster is not a risk to the fetus
- Local guidelines for treating herpes zoster in adults should be followed.

Research Initiatives for Varicella Zoster Virus Infection

- Seroreversion in vaccinees should be monitored and the need for booster immunizations evaluated
- The neurodevelopmental effect of varicella *in utero* and herpes zoster early in life should be assessed
- As newer antivirals become available, their clinical efficacy in treating varicella-associated conditions in pregnant women and neonates should be evaluated.

Epidemiology and Natural History of Herpes Simplex Virus Infection in Pregnancy

Epidemiology of Genital Herpes in Pregnant Women and Neonatal Herpes

In most countries, herpes simplex virus type 2 (HSV-2) is the most common cause of primary genital herpes although in some countries (e.g. Japan), HSV-1 is a more frequent cause of the disease.[1] Both viruses can cause neonatal herpes; up to 70% of cases are due to HSV-2[2] which is associated with a poorer prognosis than HSV-1.[3,4] To gain an appreciation of neonatal herpes, the epidemiology of infections with both HSV types should be considered.

HSV-1 infection

Primary HSV-1 infection is common in childhood. The prevalence of HSV-1 antibody increases with age and correlates with socioeconomic status.[5] Higher rates of seropositivity are seen in lower socioeconomic groups, presumably due to crowded living conditions that can provide more direct contact with infected individuals. Differences in the epidemiology of HSV-1 between countries are also apparent. For example, among 16-year-old Swedish females, the HSV-1 seroprevalence rate was 41%,[6] whereas in Ugandan villagers aged 15–19 years, the HSV-1 seropositivity rate was 95%.[7]

As with HSV-1 seroprevalence in the general population, HSV-1 seropositivity rates in pregnant women differ between countries. Serological surveys of pregnant women in the mid-1980s found that more than 90% of African-Americans in Atlanta (USA), Caucasians in Spain and Italy, and Orientals in Taipei (Republic of China) were HSV-1 seropositive. The rate was 70–80% in Reykjavik (Iceland), Lyon (France) and Sydney (Australia) and 60% in Sweden.[8] Differences within countries may also occur; from 1985 to 1989, the HSV-1 seroprevalence in Tokyo (Japan) was 50% compared with 73% in Kogoshima (Japan).[9]

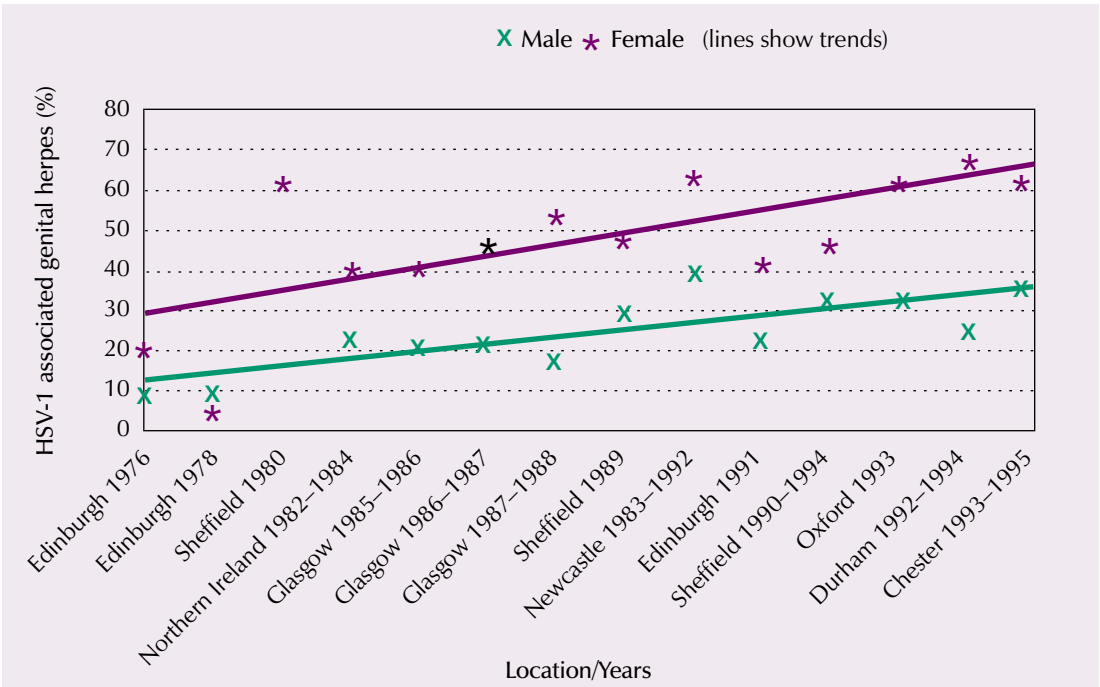

Figure 1: Increase in prevalence of HSV-1 associated genital herpes in the UK

The estimated risk of HSV-1 seroconversion during pregnancy is 2.3% in Seattle, USA.[10] However, this rate may not be generally applicable, especially as the epidemiology of HSV-1 infection is changing, with acquisition of HSV-1 occurring later in life. Improvements in socioeconomic status have been suggested to account for this age-specific decrease in the incidence of HSV-1 infection. This has been accompanied by a trend for genital HSV-1 infections to occur later in life in the UK and Northern Ireland (Figure 1), Norway and Japan, which may be partly attributable to infection resulting from orogenital contact.[11–17] In many of these studies, HSV-1 isolates predominated in first episodes in women, but the proportion of HSV-1 isolates from recurrences was generally less than 20%.[14]

HSV-2 infection

HSV-2 infection is usually acquired through sexual contact. Consequently, its prevalence increases with age and number of sexual partners. Higher rates are also observed in certain ethnic groups and lower socioeconomic groups. The sociocultural influences on these factors mean that there are widespread variations in HSV-2 seroprevalence throughout the world. For example, HSV-2 seroprevalence of the general population in the USA is 21.9%[18] whereas in a different, selected population, namely UK blood donors, the prevalence of HSV-2 antibodies was 7.6%.[19] Similarly, the seroprevalence of HSV-2 among pregnant women varies greatly throughout the world, ranging from about 7% to 33% (Table 1).

The prevalence of HSV-2 infection is increasing in some areas of the world.[18] For example, since the late 1970s, the seroprevalence of HSV-2 in the USA has increased by 30%; the age-adjusted seroprevalence increased from 16.0% in 1976–1980 to 20.8% in 1988–1994.[18]

Several studies conducted in different populations have assessed the rate of HSV acquisition. In a prospective study of low-risk college students in Columbia, South Carolina, USA, the annual rate of HSV-2 infection was approximately 2% over 4 years.[20] In comparison, in a high-risk population (STD clinic attendees in Seattle, Washington, USA), the annual rate of acquisition was 3%.[21] Other studies indicate that genital HSV infection occurs at an incidence of about 1% annually.[22,23] The transmission rate of HSV-2 has also been addressed in prospective studies of serologically discordant couples in which one partner had HSV infection and the other did not. These studies show that the transmission rate is 8–12% per year[24–26] and that women have higher rates of acquisition than men; in one study, the acquisition rate among seronegative women approached 30% per year.[25]

Population	HSV-2 seroprevalence (%)	Year	Reference
Sydney, Australia	14	1990s	27
Lyon, France	17.3	1986	8
Reykjavik, Iceland	18.8	1985	8
Padua, Italy	8.4	1985–86	8
Tokyo, Japan	6.7	1988	8
Seville, Spain	9.7	1985–86	8
Malmö, Sweden	21	1970–73	28
	21	1979	28
	25	1987–89	28
	21	1990–91	28
Stockholm, Sweden	17	1969	29
	32	1983	29
	33	1989	29
London, UK	10.4	1980–81	30
Seattle, USA	17	1989–93	10

Table 1: Prevalence of HSV-2 infection in pregnant women in different populations worldwide

Prospective studies indicate that, adjusted for the entire gestation, the rate of HSV-2 seroconversion is 0.2–2.5%, although most seroconversions are asymptomatic and unrecognized.[10,31–33] In one of the largest studies, 2% of susceptible women acquired HSV-2 during pregnancy.[10] The rate of HSV-2 acquisition in pregnancy varies between populations: in North Carolina (USA) it was 0.2% compared with 2.5% in Birmingham, Alabama (USA).[33] These studies have been conducted in the USA and there is a need to gather similar data in other regions of the world.

The acquisition rate is different if an individual is previously infected with HSV-1 versus HSV-2 as demonstrated in a study conducted in Seattle, Washington, USA. In HSV-seronegative women with HSV-2 positive partners, the acquisition rate was 33% whereas an HSV-1 positive woman with a HSV-2 positive partner had a 5% chance of acquiring HSV-2 during pregnancy.[10] A seronegative woman with an HSV-1 seropositive partner had a 4% chance of acquiring HSV-1 although not all of these infections were genital.[10]

Pregnant women can be infected with HSV at any time during gestation.[10] This has management implications as the effects of HSV on the neonate are greatest if primary infection occurs near delivery. In a large cohort study of 7046 women in Seattle, Washington, USA, one-third acquired infection during the first trimester, one-third in the second and one-third in the third trimester.[10]

Neonatal herpes

The prevalence of neonatal HSV infection varies from country to country (Table 2). In the UK, the infection is considered rare, affecting approximately 1 in 60 000 live births.[34] In comparison, the prevalence in the USA is estimated to be 1 in 1800–5000 live births.[31,35] However, the true scale of infection is probably higher due to under-reporting and difficulties in recognizing the condition. Importantly, the definition of neonatal herpes differs between countries (e.g. skin, eye and mouth [SEM] disease is sometimes excluded from the definition of neonatal herpes). These differences in definition may account for some of the variabilities in incidence of neonatal herpes reported between countries.

Country	Population	Rate of neonatal herpes	Reference
Australia		1 in 10 000–11 000	36, 37
Denmark	National	1977–1984: 1 in 42 000 1985–1991: 1 in 22 000	38
Japan	National	1 in 14 000–20 000	39
The Netherlands	National	1981–1986: 1 in 35 000 1987–1992: 1 in 35 000	40, 41
Norway	National (only HSV in cerebrospinal fluid)	1 in 25 000	
Sweden	Stockholm	1 in 15 000	42
UK	National voluntary reporting	1 in 60 000	34
USA	Seattle, Washington	1 in 1800	31
USA	California	1 in 8700	43

Table 2: Prevalence of neonatal herpes

The increasing HSV-2 seroprevalence in the USA[18] has been accompanied by a rise in the incidence of neonatal HSV infection.[35] In King County, Washington, USA, the number of cases reported per 100 000 live births increased from 2.6 in 1966–1969 to 13.4 in 1982–1983.[35]

It has been suggested that the greater tendency for primary genital HSV-1 infection in the UK[11–13,15–17] influences the type of neonatal infection (i.e. extent and severity) and may explain why similar proportions of HSV-1 and HSV-2 neonatal infections are reported in the UK.[34] This is supported by observations that 40% of primary genital herpes in Tokyo is due to HSV-1,[44] and that HSV-1 is commonly associated with neonatal herpes in Japan.[45] In contrast, in the USA where the majority of neonatal herpes is caused by HSV-2,[33] HSV-1 accounts for less than 10% of primary genital HSV infections.[8,46] However, in a more recent study, 32% of primary genital herpes in the USA was due to HSV-1.[47]

Transmission of HSV to the Fetus and Neonate

HSV can be transmitted to the fetus at one of three stages: intra-uterine, perinatally and post-natally.

Intra-uterine infection

Intra-uterine infections comprise 5–8% of all cases of neonatal herpes and can result from transplacental HSV transmission or an ascending HSV infection from the cervix.[48,49]

Perinatal infection

The main risk of HSV transmission to the neonate is at term during vaginal delivery; perinatal infection accounts for approximately 85% of all cases of neonatal herpes. The most common source of HSV in perinatal infection is the birth canal. As the neonate passes through the birth canal, it comes into contact with infected secretions; the site of entry for the virus is usually the eye, nasopharynx or an abrasion secondary to scalp electrodes or forceps. There are various sites of HSV shedding in the birth canal,[50,51] and it is likely that cervicovaginal shedding poses a greater risk than that from the vulva because the neonate is in close contact with the vaginal mucosa for several hours, but is only in light and transient contact with the vulva during delivery.[52] Fetal scalp electrodes may increase the risk of neonatal HSV infection by creating a break in the integrity of the skin through which the virus can enter the body.[31,53]

Post-natal infection

Post-natal infection with HSV accounts for 8–10% of cases[49] and is the consequence of contact with an environmental source of HSV. The documented sources of post-natal HSV infection include infected breast milk, HSV-1 oral lesions (although lesions on the thigh and breast have been implicated), and HSV-1 lesions on fathers, other family members and medical staff.[54]

Asymptomatic and Symptomatic Virus Shedding in Neonatal Herpes

The transmission of HSV to the neonate can occur both when there are symptomatic maternal recurrences or episodes of asymptomatic virus shedding. The latter occurs in the genital tract during labour as a consequence of virus reactivation or acquisition of genital herpes during pregnancy.[10,31,55] The rate of asymptomatic shedding at labour measured by HSV culture varies from 0.35% to 1.4% and is no higher than at other times in the pregnancy.[10,31]

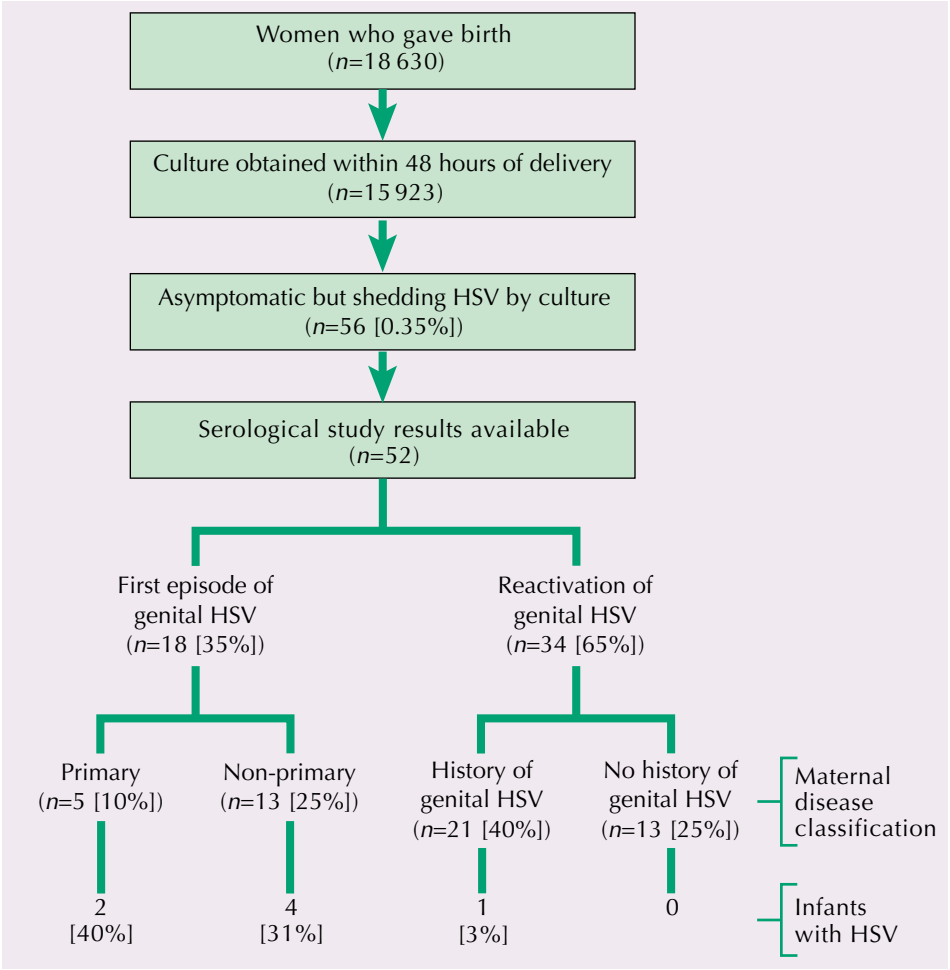

Figure 2: HSV transmission among women with asymptomatic shedding during labour[31]

In a large prospective study conducted in Seattle, Washington, USA, 15 923 asymptomatic women had cervical and vulval swabs taken within 48 hours of labour. In total, 56 women (0.35%) were found to be shedding HSV in the absence of symptoms and a further 99 women (1.2%) shedding in the presence of symptoms; thus asymptomatic virus shedding accounted for 23% (56/155) of all shedding. Of the 56 women exhibiting asymptomatic virus shedding, serological testing for HSV-1 and HSV-2 revealed that 65% had evidence of genital HSV reactivation and 35% had recently acquired infection (Figure 2).[31] In a subsequent study, serum samples obtained from 7046 pregnant women at risk of HSV infection were tested for HSV-1 and HSV-2 antibodies at their first antenatal visit and again at delivery; these results were correlated with the occurrence of antenatal genital infections. Seroconversion was noted in 94 women (1.3%) and 34 (64%) of these women had symptoms consistent with genital herpes.[10] In another study of 414 pregnant women with a history of HSV infection who were swabbed at delivery, five of 354 who had no apparent signs or symptoms of infection shed virus (1.4%).[56]

As discussed, neonatal herpes most commonly results from contact between the newborn and infected secretions in the birth canal of an asymptomatic mother. One study indicates that 70% of infants with neonatal HSV infection were infected by mothers in whom there was asymptomatic shedding of HSV at the time of delivery usually, in women who had recently acquired HSV.[31] In the general population, only one in five people who are HSV-2 seropositive have received a diagnosis of genital herpes. Of the remainder, 60% are not recognized clinically as having the disease and 20% will have truly asymptomatic infection. Thus, the under-recognition and under-diagnosis of genital herpes impedes effective management of neonatal herpes.

Factors Influencing Fetal Acquisition of HSV and Impact of Infection

There are several factors that influence acquisition of infection by the fetus, including:

- Primary versus recurrent maternal infection
- Discordancy of partners
- Maternal antibody titre
- Invasive obstetrical procedures.

Primary versus recurrent HSV and risk of neonatal infection

Primary symptomatic and asymptomatic maternal HSV infection near delivery carries a greater risk to the newborn than recurrences of maternal genital herpes. The relative risk of HSV transmission associated with first episode maternal disease has been established in a large prospective study conducted in the USA.[31] A total of 15 923 pregnant women in early labour who had no symptoms or signs of genital herpes were followed and the risk of HSV transmission to the neonate was evaluated. Neonatal herpes developed in six out of 18 infants born to women with recently acquired, subclinical first episode genital HSV (i.e. women with HSV-1 antibodies in an initial serum sample and from whom HSV-2 was isolated in early labour and who were seropositive for HSV-2 in a subsequent sample) compared with only one of 34 (3%) infants born to women with recurrent disease ($P<0.01$), (Figure 2).[31]

Other studies also document a lower rate of HSV transmission in mothers with recurrent infection. In 34 cases of vaginal delivery in which the women had asymptomatic or symptomatic genital herpes recurrences (56% with lesions at delivery), none of the 34 infants developed neonatal herpes.[26] In 414 pregnant women with a history of genital herpes, there were 10 vaginal deliveries following reactivation but none of the neonates were infected with HSV.[56] A retrospective study in Denmark in 1977–1991 identified 30 cases of neonatal herpes from hospital records of 862 298 deliveries (i.e. one in 29 000 live births).[38] Three mothers (10%) had recurrent genital herpes at delivery, three (10%) had primary genital herpes and five (17%) had oral herpes, whereas the type of infection was undetermined for the remainder. Only one neonate out of three had serious sequelae following a recognized maternal herpes recurrence compared with two out of three children born to mothers with documented primary infection.[38]

An analysis of five studies of genital herpes in pregnancy has also shown that presentation with first episode genital herpes in pregnancy is associated with a higher risk of transmission during delivery.[57] The overall transmission rate in these studies was 19/46 or 41%.[57] Overall, these studies have found that the risk of neonatal herpes to the infant from a woman with primary HSV infection is 50%; for HSV-2 infection from a woman with prior HSV-1 infection and new HSV-2 infection the risk is 20%, and the risk of neonatal transmission with recurrent HSV infection is less than 1%.[10,26] Importantly, whether or not the mother has pre-existing antibodies to HSV-1, the outcome for a neonate whose mother has primary genital HSV-2 near term is similar.[31]

Taken together, the studies show that the infants of women shedding HSV as a result of recently acquired genital HSV infection are at higher risk for acquisition of neonatal HSV infection than those of women with HSV reactivation. Importantly, the risk of virus transmission is greatest if a woman has the first episode of genital herpes near the time of delivery.[31]

Natural history studies of genital HSV infection during pregnancy indicate that women who have first episode disease are more likely to have cervical infection and to shed larger amounts of virus for a longer period than women with a recurrence of genital herpes.[31,58] The increased virus load may in part account for the higher rate of transmission of HSV to the neonate in maternal primary genital herpes compared with recurrent genital herpes.

Maternal antibody titre

High titres of type-specific neutralizing antibody in the neonate convey some, albeit not total, protection and are associated with a lower risk of neonatal infection. There are significant differences in HSV antibody titres between neonates exposed to HSV at delivery who remain well (high levels of antibody) and those who develop neonatal HSV infection (low levels of antibody). This provides evidence of the protective effect of antibodies[26,59,60] (Figure 3). The likelihood of neonatal herpes may be a function of the time it takes to elicit a mature antibody response; if the mother develops primary genital herpes during the third trimester, maternal or neonatal antibodies to HSV may not develop rapidly enough to protect the infant against infection. The titre is also related to disease presentation with the highest levels seen in SEM disease, lower levels in central nervous system (CNS) disease and very low levels detected in disseminated disease.

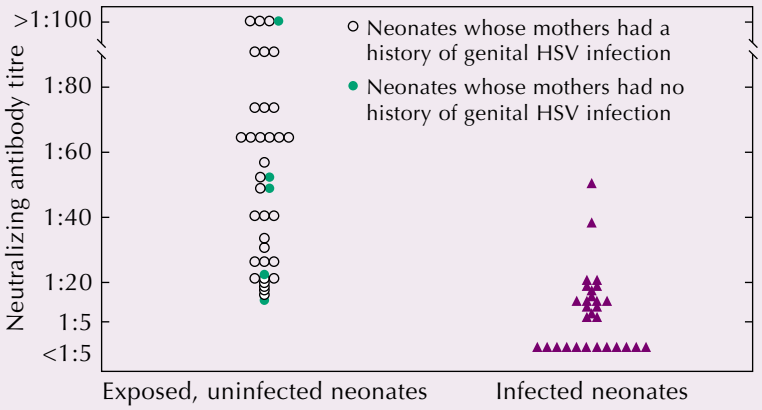

Figure 3: Neutralizing antibody titres in infants exposed to HSV during vaginal delivery[26]

Invasive obstetrical procedures

The risk of neonatal HSV infection has been associated with the use of invasive procedures. Cases of neonatal HSV encephalitis secondary to the application of fetal scalp electrode have been reported[53] and in a large retrospective study, an increased risk of neonatal HSV was associated with their use.[31] An additional factor associated with disease acquisition is a long duration of ruptured membranes.[10] Thus, invasive obstetrical procedures, such as electronic fetal monitoring scalp electrodes, early artificial rupture of the fetal membranes, forceps or vacuum extractors should be restricted.

Discordancy of partners

The HSV-seronegative woman is at risk for acquisition of HSV if her partner is seropositive.[10,61] As the consequences of infection during pregnancy can be serious, a woman should be asked about any history of genital herpes and whether her sexual partner(s) has (have) genital herpes. In a study of 194 serologically discordant couples, the annual rate of genital HSV acquisition was 31.8% in susceptible female partners lacking HSV-1 or HSV-2 antibodies.[61] In those women with prior HSV-1 infection, the annual rate of acquisition was 9.1%.[61]

Impact of HSV Infection on the Pregnant Woman and Neonate

Maternal infection

HSV-2 infection is most often localized to the genitals in the infected mother and the clinical disease is self-limiting. An uncommon complication in the pregnant woman is widely disseminated HSV infection involving cutaneous dissemination and visceral sites. It leads to serious illness that, if left untreated, has a mortality rate of more than 50%.[32,62,63]

Fetal and neonatal infection

In contrast to the relatively rare cases of disseminated infection in the mother, HSV infection more often has serious consequences for the fetus and neonate. Transplacental transmission before week 20 of pregnancy can manifest as spontaneous abortion in up to 25% of cases.[32,48,64]

Infection that occurs later in pregnancy is not associated with a greater incidence of spontaneous miscarriages.[10,52,64] Intra-uterine infections may also be evident as skin scarring or lesions, chorioretinitis or brain malformation (e.g. microcephaly, hydrocephalus) at birth.[33,48]

Symptomatic and asymptomatic first episode genital herpes during late pregnancy may be associated with prematurity and fetal growth restriction.[50,58] This relationship was established in two small case control studies but was not confirmed in a larger study in which the frequency of complications was low both among women who seroconverted and those who did not.[10] Thus, it is possible that HSV infection has an effect on pregnancy that could be demonstrated only by larger cohort studies.[10] In contrast, asymptomatic recurrent disease is not associated with an increased risk of prematurity or decreased birth weight.[10,51,56,58] Infants of women with asymptomatic shedding who recently acquired genital HSV infection were more likely to be premature (75% delivered before 37 weeks of pregnancy) and have lower birth weight than the infants of mothers shedding virus during an episode of recurrent genital HSV.[58]

Classification and prognosis of neonatal herpes

The clinical presentation and classification of infants with neonatal HSV infection into one of three categories reflects the site and extent of virus replication. The classification of infected neonates is mandatory for prognostic and therapeutic considerations:

- SEM infection
- CNS involvement (encephalitis) with or without SEM infection
- Disseminated infection with or without SEM infection.

The incidence, morbidity and mortality of each neonatal herpes manifestation differ considerably (Table 3).

Category	%	Mortality	Morbidity (neurologically impaired)
Disseminated	40	90%	≥95%
CNS infection (encephalitis)	40	75%	49–67%
SEM	20	Uncommon	30%

Table 3: Presentation, incidence and outcome in untreated neonatal herpes

Disseminated infection

Neonates with disseminated infection have the worst prognosis. The disease involves multiple organs, especially the lung, liver, adrenal glands and brain. Encephalitis is a common manifestation of disseminated infection, occurring in about 60–75% of untreated children. Mortality in the absence of therapy exceeds 80% and nearly all survivors are impaired.[33]

CNS infection (encephalitis)

Approximately one-third of all infants with neonatal herpes have CNS infection only. It is thought that this represents axonal transmission of virus to the CNS. In contrast, in infants with disseminated infection, the brain is probably seeded by a blood-borne route which results in multiple areas of necrosis. In infants with CNS infection who are not treated, the mortality rate is 50%.[33] The long-term prognosis is poor with most survivors suffering neurological impairment.

SEM infection

SEM disease is rarely fatal but can be associated with morbidity. Approximately 30% of these children will eventually exhibit evidence of neurological impairment; significant findings

include spastic quadriplegia, microcephaly and blindness. It is likely that a widely distributed skin rash reflects widespread viraemia that can lead to the seeding of organs such as the brain. Although these infants appear healthy at birth, insidious reactivation in vital organs results in impairment. As neurological impairment becomes apparent between 6 months and 1 year of life, infants with SEM should be carefully followed.[65] Recent data suggest that such infants are PCR-positive for HSV DNA in their CNS. Thus, subclinical CNS infection may explain these neurological deficits.

Infants who have SEM disease will often have recurrences. Results from a small study suggest that the number of recurrences of vesicles in the first 6 months of life is predictive of neurological outcome.[4] In the study, among infants with HSV-2 SEM infection, four (29%) of 14 infants with three or more recurrences of skin vesicles in the first 6 months of life developed neurological impairment compared with none of 15 infants who experienced fewer than three cutaneous recurrences (P=0.04).[4]

Predictors of morbidity and mortality

Factors that influence morbidity and mortality have been established in a prospective study of 202 infants with confirmed neonatal herpes.[4] Mortality was significantly higher in neonates with a decreased level of consciousness at the start of therapy, those who had disseminated intravascular coagulopathy, or who were premature. In infants with disseminated disease, HSV pneumonitis was associated with greater mortality (Table 4).[4]

Clinical characteristic	Relative risk
Decreased level of consciousness at the start of therapy	5.2
Disseminated intravascular coagulopathy with disseminated disease	3.8
Prematurity	3.7
HSV pneumonitis in infants with disseminated disease	3.6

Table 4: Clinical characteristics predictive of mortality in neonatal herpes[4]

In those children who survived, morbidity (impairment of normal function at 12 months) was most frequent in individuals with CNS disease, disseminated infection, seizures or infection with HSV-2 (Table 5).[4]

Clinical characteristic	Relative risk
CNS disease	4.4
Disseminated infection	2.1
Seizures	3.0
Infection with HSV-2	4.9

Table 5: Clinical characteristics predictive of morbidity in neonatal herpes[4]

Conclusions

The epidemiology and natural history of neonatal herpes dictate the management of both the pregnant woman and the neonate. Factors that influence acquisition of HSV by the neonate include whether maternal infection is primary or recurrent, use of invasive obstetrical measures (e.g. fetal scalp electrodes) and maternal antibody titre. Thus, any management protocol must take account of these different elements, each of which contributes to the risk of neonatal herpes.

The site and extent of HSV replication influences the clinical presentation and classification of infants with neonatal herpes. The classification of infants with neonatal herpes into one of three categories is vital for prognostic purposes and dictates the therapeutic approach for an infant.

With the increasing prevalence of neonatal herpes, especially in the USA, physicians should continue to consider its possibility so that early diagnosis can lead to prompt treatment.

Summary

The incidence of neonatal herpes varies throughout the world, ranging from one in 1800 to one in 60 000. The reasons for these variations are unknown but may reflect differences in HSV seroprevalence.

Neonatal herpes is most commonly acquired through perinatal contact with HSV-infected secretions in the birth canal. It is estimated that 5% of cases are the consequence of intra-uterine transmission and that in 10% HSV is acquired post-natally.

Seventy per cent of infants with neonatal herpes are born to mothers with asymptomatic HSV infection.

The risk of the neonate acquiring neonatal herpes is influenced by several factors, the most important of which is whether maternal genital disease is primary or recurrent. The risk of transmission is greatest if a formerly seronegative woman has a first episode of genital herpes near the time of delivery. Another important risk factor is maternal HSV antibody titre, high titres of type-specific neutralizing antibody appear to be protective. Other risk factors include the use of invasive obstetric procedures including fetal scalp electrodes and membrane rupture of long duration.

Intra-uterine HSV infection can manifest during the first half of pregnancy as spontaneous abortion or as scarring, chorioretinitis or brain malformations. Symptomatic and asymptomatic primary disease may be associated with prematurity and fetal growth restriction, but any relationship must be confirmed by large cohort studies. In comparison, asymptomatic recurrent disease is not associated with an increased risk of either prematurity or low birth weight.

Management of Herpes Simplex Virus Infection in the Pregnant Woman

Diagnosis of Genital Herpes Simplex Virus Infection in the Pregnant Woman

As most of the clinical manifestations of recurrent genital herpes are similar in non-pregnant and pregnant women,[51,58] the diagnosis of herpes simplex virus (HSV) infection in pregnancy should follow the guidelines for the diagnosis of the infection discussed in the *IHMF Management Strategies* publication: *Progress with diagnostic tests and vaccines for alpha-herpesviruses*.

Distinguishing primary and recurrent infection

Definitive classification of genital HSV infection during pregnancy can be accomplished only where clinical evaluation is accompanied by virus culture and type-specific serological testing.[66] Detailed and simple histories both have low specificity and sensitivity for diagnosis of genital herpes during pregnancy; in one study of 201 women, 9.0% gave no history of genital herpes although 30.4% were HSV-2 seropositive.[67] Another complicating factor is that, although the typical clinical manifestations of primary genital herpes are generally more severe and prolonged than those associated with recurrences, there is substantial overlap.[68,69] In a study of 23 women with symptoms clinically suggestive of primary infection in their second or third trimester, 22 had recurrent or non-primary infection as confirmed by type-specific serology or virus culture.[66] Similar findings were reported in a study of 498 patients presenting with signs and symptoms of first episode genital herpes.[70] Even with experienced clinicians, almost 10% of those they judged to have first episode disease had evidence of HSV-2 infection acquired a long time before the apparent first episode.[70] Thus, appropriate testing must be used for accurate identification of primary HSV infection in pregnancy.[66,70]

Weekly virus cultures

The use of weekly HSV cultures prior to delivery in pregnant women with a history of genital herpes is not warranted. Antepartum cultures do not predict an infant's risk of acquisition of HSV at delivery[56] as there is no correlation between antenatal recurrences, or virus shedding, and the presence of virus shedding at term.[10,71] Additionally, because the virus titre in asymptomatic shedding episodes is 10–100 times less than in symptomatic episodes,[72] the sensitivity of virus culture for detecting HSV infection in asymptomatic individuals is likely to be low. Also, virus culture is time-consuming, with less than half of results being available within 24 hours.[73–75] Rapid assays such as ELISA may have similar sensitivity to virus culture, but have reduced sensitivity for detecting asymptomatic virus shedding compared with symptomatic shedding. In addition, as shedding at delivery is relatively rare, currently available assays occasionally give false positives and thus the use of these assays to screen populations with low prevalence of infection means positive results have low predictive value for infection.

Management of Genital Herpes in Pregnancy

If genital HSV infection is acquired during pregnancy, it is necessary to reduce the risk of transmission to the neonate during delivery. Caesarean section is one strategy for management and antiviral therapy is another potential option, which is currently being evaluated in clinical trials.

Antiviral treatment in pregnancy

There are insufficient data to recommend the routine use of antiherpes therapy for any indication in pregnant women; the potential benefits of treatment should be balanced against the potential adverse outcomes for both mother and fetus. All patients should be advised that, in common with the vast majority of drugs, aciclovir, valaciclovir or famciclovir are not specifically licensed for any indication in pregnancy. Although routine antiviral therapy is not required for genital herpes in pregnancy, it may be administered for disseminated disease or presumed maternal primary infection. For this reason, it is important to characterize a first episode (e.g. primary versus non-primary) in a woman presenting in the third trimester. Intravenous aciclovir should be initiated in women who have evidence of disseminated infection. Prophylaxis with oral aciclovir or any other antiherpes agent is not currently recommended during the third trimester for women with known recurrences. Studies of this strategy are underway and their results may influence the approach to treating recurrences in pregnancy.

Safety

Aciclovir: Healthcare providers are encouraged to report all pregnancy exposures to the manufacturers as for other drugs used in pregnancy.

The main concern with use of any drug during pregnancy is teratogenicity. *The Aciclovir and Valaciclovir Pregnancy Registry* was established to monitor any potentially teratogenic effects of aciclovir. Before it was closed, the Registry collected data for over 1200 women exposed to any formulation or dose of aciclovir, including valaciclovir, during pregnancy (Table 1).

- Data from the *Aciclovir and Valaciclovir Pregnancy Registry* provide assurance to women already exposed inadvertently to aciclovir in the first trimester
- Findings to date do not indicate an increase in risk for major birth defects with aciclovir compared with those expected in the general population
- In the presence of maternal HSV infection life-threatening to neonate, intravenous aciclovir may be indicated
- Routine administration of aciclovir to pregnant women who have a history of recurrent genital herpes is not currently recommended. Trials are ongoing and their results may influence the approach

Table 1: Summary of recommendations for aciclovir use in pregnancy

As of December 1997, no apparent adverse effects had been ascribed to aciclovir use during pregnancy.[76] The results were based on 1129 pregnancy outcomes recorded in the Registry with two-thirds (712) of exposures in the first trimester. In an earlier analysis of the Registry data,[77] 21 birth defects were recorded (2.2%), which is similar to the 2–7% rate observed in the general population.[78,79] The rate of birth defects in the first trimester following aciclovir exposure was 3.0% (15/493 [95% confidence interval (CI) 1.8–5.1%]), which is also within the range observed in the general population.[77] Additionally, the birth defects reported to the *Aciclovir and Valaciclovir Pregnancy Registry* do not show a pattern suggestive of a common aetiology.

In reviewing the data from the *Aciclovir and Valaciclovir Pregnancy Registry*, the *Centers for Disease Control* (CDC) considers that the number of pregnancies evaluated is insufficient to draw definitive conclusions about the risks associated with aciclovir during pregnancy.[78] In considering the risks, as the kidney eliminates aciclovir, it is important to confirm whether there is any renal risk to the fetus; ongoing studies should answer this question.

Newer antivirals: There are very few data on the safety of newer antivirals in pregnant women. In non-pregnant adults, the bioavailability of aciclovir after the oral administration of valaciclovir is 3–5 times greater than that after the administration of oral aciclovir.[80] In a study comparing oral valaciclovir (500 mg twice daily) with oral aciclovir (400 mg three times daily)

from 36 weeks' gestation, valaciclovir demonstrated higher bioavailability than aciclovir, with no aciclovir accumulation in the fetus (maternal/infant plasma ratio: valaciclovir=1.7; aciclovir=1.3).[81,82] Despite the extensive physiological changes in pregnancy, the pharmacokinetic values for aciclovir and valaciclovir were similar to those reported in non-pregnant adults.[82] This finding is supported by studies with aciclovir which also demonstrated similar pharmacokinetic values for women in late pregnancy and in non-pregnant adults.[81,83] In the pharmacokinetic study of valaciclovir in pregnant women, none of the study participants had either genital HSV recurrence or asymptomatic virus shedding at delivery.[82] There are no substantial data on the safety of penciclovir or famciclovir during pregnancy.[84]

Efficacy

It is well established that in non-pregnant women, aciclovir shortens the duration and lessens the severity of symptoms of a genital herpes episode as well as decreasing the duration of virus shedding,[68,85] but there has been a limited number of studies evaluating aciclovir in pregnancy. In a randomized, double-blind, prospective study, aciclovir reduced the number of positive virus cultures at delivery in women with first episode genital herpes at any time during pregnancy and, hence, the need for Caesarean section.[86] The effect of oral suppressive aciclovir therapy (200 mg four times daily) from 36 weeks' gestation to delivery was compared with placebo in 46 pregnant women who presented with first episode genital herpes during pregnancy.[86] The protocol permitted vaginal delivery if there was no evidence of lesions; otherwise a Caesarean section was performed. At delivery, none of the 21 women treated with aciclovir had clinical evidence of recurrent genital herpes compared with nine of 25 women (36%) in the placebo group (P=0.002), (Table 2),[86] and this was reflected in the proportion of Caesarean sections (P=0.002). No women in either treatment group experienced asymptomatic virus shedding at delivery and no infants had neonatal herpes or suffered any adverse effects due to treatment.

	Aciclovir *n*=21 (%)	Placebo *n*=25 (%)	*P* value
Clinical recurrences	0 (0)	9 (36)	0.002
Caesarean sections for HSV	0 (0)	9 (36)	0.002
Overall rate of Caesarean sections	4 (19)	10 (40)	
Neonatal herpes	0	0	

Note: includes women non-compliant with regimen

Table 2: Effect of aciclovir on clinical recurrences, number of Caesarean sections, cases of neonatal herpes and HSV shedding in pregnant women[86]

Another randomized, placebo-controlled trial of suppressive aciclovir (200 mg four times per day) during late pregnancy in 63 women with recurrent genital herpes demonstrated that aciclovir significantly reduced the number of clinical recurrences.[87] The trial was too small to demonstrate conclusively a difference between aciclovir and placebo on the rate of Caesarean section, although there was a trend towards fewer Caesarean sections with treatment (Table 3).[87] Of note is that two women who were receiving aciclovir had a clinical recurrence during labour.

In a non-randomized, uncontrolled study, aciclovir reduced symptomatic recurrences and virus shedding in pregnant women with recurrent genital herpes.[88] A total of 46 women received aciclovir 200 mg four times daily generally within 1 week before expected term and an unmatched cohort of 46 women were untreated. Aciclovir was given for an average of 10 days (range 3–27 days). No woman in the aciclovir group had a symptomatic recurrence during treatment, excreted virus during delivery or required Caesarean section because of herpes. In contrast, 12 (26%) untreated women had symptomatic recurrences within 10 days of delivery (Table 4).[88] Of these 12 women, nine had a Caesarean section because of herpes.[88]

	Aciclovir (*n*=31)	Placebo (*n*=32)	Odds ratio (95% CI)
Clinical recurrence after trial entry	1	8	0.10 (0.00–0.86)
Clinical recurrence at time of labour	2	6	0.30 (0.03–1.9)
Caesarean section for HSV	4	8	0.44 (0.09–1.94)
Caesarean section for other reasons	3	2	1.61 (0.17–20.43)
Total Caesarean sections	7	10	0.64 (0.18–2.27)
Infants with neonatal herpes	0	0	

Table 3: Pregnancy outcome in a randomized, placebo-controlled trial of aciclovir[87]

Outcome	Aciclovir (*n*=46)	No treatment (*n*=46)
HSV recurrence/positive culture		
<10 days before delivery	0	8 (17%)
During delivery	0	4 (9%)
Total	0	12 (26%)
Caesarean section for		
Herpes	0	9 (20%)
Obstetric reasons	6 (13%)	6 (13%)
Total	6 (13%)	15 (33%)

Table 4: Recurrences and Caesarean section in an uncontrolled trial of aciclovir in late pregnancy[88]

Overall, these trials in pregnant women suggest that aciclovir may reduce the clinical recurrence rate and lower the Caesarean section rate. However, the sample sizes are too small for definitive conclusions to be drawn. In the USA, three studies of HSV suppression for women in late pregnancy with known recurrences or third trimester presumed primary infection are underway. There have been no trials of intrapartum antiviral therapy in women with recurrent infection; large scale trials of the impact of this strategy on neonatal herpes are required.

There are several studies exploring the use of valaciclovir in pregnancy. Among them is a study of the effect of valaciclovir 500 mg twice daily on shedding and recurrence rate. Another ongoing randomized, double-blind trial is assessing valaciclovir 500 mg or 1000 mg once daily from 36 weeks on Caesarean section rates and recurrence rates.

Economic analysis of antiviral treatment

Economic modelling of suppressive aciclovir from 36 weeks' gestation shows that it is cost-effective compared with no therapy in the management of recurrent genital herpes in pregnancy.[89] The model used was based on USA treatment practices and costs, and it was assumed that vaginal delivery would take place if no recurrence was present. In the analysis, the estimates of HSV recurrence risk and likelihood of Caesarean section in aciclovir-treated patients used were derived from a literature review and the authors' own prospective surveillance.[89]

Suppressive aciclovir from 36 weeks' gestation decreased the average cost for obstetrical care and delivery, primarily by decreasing the costs associated with Caesarean section.[89] Treatment of pregnant women with a history of HSV recurrences resulted in estimated average savings of US$183 per patient or US$36.6 million per year at a national level. For a pregnant women with first episode herpes or frequent recurrences (six or more reactivations per year), the cost

savings were greater: US$455 and US$391, respectively. The analysis did not include the indirect costs associated with Caesarean deliveries (e.g. increased morbidity and mortality); it was anticipated that if these had been incorporated, the cost savings with aciclovir would have been much higher. Moreover, the analysis used conservative estimates of compliance with antiviral therapy and efficacy of Caesarean delivery.

Caesarean section

Elective Caesarean section before the onset of labour or the rupture of membranes has the potential to reduce exposure of the neonate to HSV in the birth canal. At present, the evidence for the effectiveness of this intervention is limited and it has not been evaluated in controlled trials. A protective effect of Caesarean section is suggested by small, uncontrolled studies in women with positive genital cultures 1–2 weeks before delivery or with positive cervical cultures at delivery.[64,90,91] None of these studies differentiated primary from recurrent HSV infection.

Large case series suggest that Caesarean section is not completely protective for neonatal herpes; in these studies 13–33% of newborns with HSV infection were delivered by this method.[2,38,92,93] Information on the effectiveness of Caesarean delivery in women with asymptomatic genital herpes is provided from a large cohort study in which virus cultures were taken from pregnant women in early labour with or without symptoms of genital HSV infection.[31] Fourteen per cent (6/43) of neonates who had vaginal delivery became infected with HSV compared with 8% (1/13) delivered by Caesarean section (all Caesarean sections were for obstetrical reasons). It is difficult to draw firm conclusions as the sample size was not large enough to achieve statistical significance and, therefore, it is not possible to define categorically the benefit of Caesarean section in either symptomatic or asymptomatic women.

A survey conducted in Denmark estimated 414 excess Caesarean sections had to be performed for each case of neonatal herpes prevented.[38] Moreover, the study also found that of ten cases of neonatal herpes who developed serious sequelae or died, four were delivered by Caesarean section. Thus, as noted above, this method of delivery does not always protect against neonatal herpes. The mode of delivery, therefore, may be based on clinical findings at the time of delivery. The presence of herpetic lesions is a relative indication for Caesarean section.

Although Caesarean section for HSV recurrences may be advised on ethicolegal grounds (e.g. to avoid litigation) or may be requested by the woman, there is much evidence that routine Caesarean section in these cases is unnecessary. In the Netherlands, where Caesarean section for women with recurrent genital herpes lesions at delivery is no longer performed, there has been no apparent increase in the number of cases of neonatal herpes.[41] Similarly, a survey conducted in California, USA, from 1985 to 1995 found that although there was a 10% decrease in deliveries by Caesarean section, there was no change in the incidence of neonatal herpes (approximately one case per 8700 births). This lack of change in the rate of neonatal herpes was in the face of an increase in the proportion of women with a diagnosis of genital HSV infection for whom delivery was vaginal (8% in 1985 to 35% in 1995) and an almost two-fold increase in clinical diagnoses of HSV infection.[43]

These findings of an unchanged incidence of neonatal herpes, despite changes in practice, are also corroborated by a smaller USA study. A 37% decrease in Caesarean sections for women with genital herpes (from 57 Caesarean sections/90 women with genital herpes in 1984–1986 to 81/217 in 1988–1991) was reported following recommendations by the American College of Obstetrics and Gynecology in 1988. Despite this, an increased incidence of neonatal herpes was not documented.[94]

Thus, Caesarean section has been used widely but it, and other management options, should be discussed with the patient. Controlled trials of management policies to reduce the use of Caesarean section are required. The mode of delivery may be based on clinical findings at the time of delivery. The presence of herpetic lesions is only a relative indication for Caesarean section. In a woman with a primary genital HSV infection after 34 weeks, delivery by elective Caesarean section should be considered.

Economic analyses of Caesarean section

Economic analyses indicate that Caesarean delivery for women with a history of genital herpes with lesions that recur at delivery results in increased maternal morbidity and mortality at substantial financial expense compared with a vaginal delivery.[95] The analysis, which was based on a literature survey and applying 1993 USA costs, estimated that this practice resulted in more than 1580 excess Caesarean sections (i.e. performed solely for HSV infection) for every case of neonatal herpes prevented.[95] This analysis calculated a cost of US$2.5 million per case of neonatal herpes averted and a cost of US$203 000 per quality adjusted life-year (QALY). In contrast, Caesarean section for women who present with their first clinical episode of genital herpes at delivery has lower costs per neonatal benefit. It resulted in nine excess Caesarean sections per case of neonatal herpes avoided and was cost-saving (US$38 758 saved per case of neonatal herpes avoided) compared with Caesarean section for women with a history of genital herpes.[95]

The analysis determined that the strategy of Caesarean section for lesions at delivery in women with recurrent genital herpes resulted in 0.57 maternal deaths for every neonatal death prevented.[95] The estimates from the model are sensitive to the risk of vertical transmission (estimated to be 1%) and to the efficacy of Caesarean section (estimated to be 80%); reductions in either of these parameters could result in maternal deaths exceeding neonatal mortality.[95] For women with no history of genital herpes, Caesarean section for lesions at delivery would result in 0.004 maternal deaths per neonatal death prevented.[95] It is suggested that there is excessive financial costs associated with Caesarean section in women with a history of genital herpes and other strategies should be examined.[95]

Cost-effectiveness analysis of aciclovir prophylaxis and Caesarean section

Economic modelling indicates that oral aciclovir prophylaxis in late pregnancy for women with recurrent genital herpes is more cost-effective than the strategy of Caesarean delivery for all women with recurrent genital herpes who present with lesions.[96] In the analysis, clinical outcomes and direct costs were evaluated. The probabilities of clinical outcome were based on expert opinion and the literature, whereas cost data were based on hospital costs and a cohort of herpes-infected neonates.

The analysis found that to prevent one neonatal HSV infection, 1818 women with recurrent genital herpes would have to follow the strategy of aciclovir prophylaxis during late pregnancy followed by Caesarean delivery for women with genital lesions. This strategy would have an incremental cost (i.e. above no intervention) of over US$493 000 per neonatal infection prevented and US$1.1 million per neonatal death or disability prevented (Table 5).[96]

	Aciclovir prophylaxis during late pregnancy followed by Caesarean delivery for women with genital lesions	Caesarean section for genital herpes lesions at delivery
Number of women required to follow strategy to prevent one case of neonatal herpes	1818	286
Incremental cost per neonatal infection prevented (US$)	493 000	1.3 million
Incremental cost per neonatal death or disability prevented (US$)	1.1 million	3 million

Table 5: Cost-effectiveness of aciclovir prophylaxis[96]

In comparison, Caesarean section for genital herpes lesions at delivery requires 286 women with recurrent herpes to undergo Caesarean section to prevent one neonatal infection, at a

cost of more than US$1.3 million per neonatal infection prevented and more than US$3 million per neonatal death or disability prevented (Table 5).[96] If aciclovir is given and herpes lesions still occur, the incremental cost of requiring Caesarean delivery for these women over vaginal delivery with culture and follow-up of exposed infants is more than US$1.4 million per neonatal infection prevented.[96]

Prevention of Infection

The morbidity and mortality of neonatal herpes could be either reduced or avoided by preventing HSV acquisition in seronegative pregnant women, but limiting exposure to HSV-2 during pregnancy is difficult as transmission is sexual. There are a number of interventions that have potential value but their efficacy needs to be established.

Abstinence and behavioural change

For a pregnant woman who is HSV seronegative, abstinence can prevent acquisition of HSV infection but it is unlikely that couples will adhere to this behavioural intervention. In a study in which pregnant women and their partners were screened for type-specific antibodies to HSV, 10% (18 of 190) women were HSV seronegative but had seropositive partners. Of these, seven of 18 continued to have unprotected intercourse after being informed of their serological status and one of seven seroconverted during pregnancy.[97] Consequently, new approaches to counselling should be developed and their ability to change risk behaviour evaluated.

Antivirals

Clinical trials have demonstrated a significant reduction in HSV shedding with antiviral therapy which, therefore, offers a potential means of reducing HSV transmission/acquisition in discordant couples. Definitive proof of reduced transmission to partners still awaits the completion and analysis of ongoing trials; one such trial is evaluating the effect of valaciclovir (500 mg/day) versus placebo on HSV-2 transmission in discordant couples.[98] A North American trial of valaciclovir in pregnant women is ongoing and may provide evidence of the value of suppressive therapy in reducing the risk of HSV acquisition by the neonate.

Condoms

In vitro evaluations of condoms demonstrate that they provide an effective physical barrier to HSV[99,100] although their efficacy in preventing HSV transmission during sexual intercourse has not been demonstrated. Moreover, shedding and acquisition may occur at sites which are not covered by the condom.

Vaccination

There are currently no licensed vaccines for HSV. Inactivated whole virion HSV (e.g. Skinner vaccine, Lupidon vaccine, Dundarov vaccine, Kutnova vaccine, Cappell vaccine) has not been proven to be effective in well-controlled, clinical trials.[101,102] A subunit vaccine developed by the Chiron Corporation and containing HSV-2 glycoprotein (g) D and gB with the adjuvant MF59 reportedly failed to protect against HSV infection in two large clinical trials.[103]

A second subunit vaccine containing HSV-2 gD combined with the adjuvant monophosphoryl lipid A (MPL) has been developed by SmithKline Beecham Biologicals and shown to be immunogenic in man.[104,105] The vaccine is currently in a Phase III trial, the primary end-point is prevention of clinical disease.[106]

Other vaccines are also in development. A replication-impaired (disabled infectious single cycle, DISC) vaccine is in Phase II trials after proving to be immunogenic in Phase I trials.[107] Other candidate vaccines (live genetically [gamma 34.5 gene deleted] attenuated HSV) are in pre-clinical development or in Phase I clinical trials (nucleic acid [DNA] vaccines).[106]

Potential Strategies to Screen for HSV Infection

A benefit of serotesting for HSV infection is to identify seronegative pregnant women who are at risk of seroconversion. For these women, determination of serostatus may be valuable because of the risks associated with acquisition of infection in late pregnancy, although the efficacy of any intervention and the impact of knowledge of serostatus on HSV acquisition have not been established. Women identified as seronegative could be advised about the risk of acquiring HSV and the strategies for avoiding acquisition. Thus, type-specific serological testing for HSV-1 and HSV-2 may have value in the management of the pregnant woman and neonate. Depending on test performance and local epidemiology, it has the potential to identify previously infected individuals and, if samples are taken sequentially, it is possible to distinguish seroconverters. If both partners are tested, it is possible to identify discordant couples, which may help the woman understand the risk of acquiring genital herpes and its implications. It should be noted that type-specific serological testing alone cannot differentiate between genital HSV-1 infection and possible orolabial HSV-1 infection.

There are two potential strategies for identification of pregnant women at risk of HSV infection: targeted (methodical testing of at-risk populations) and universal (broad) testing. The relative merits of these two approaches have not yet been fully defined. Universal testing has the advantage that, as everyone would be tested, there may be destigmatization of genital herpes. However, it would be necessary to test many people who are at very low risk. This not only has a potential economic cost but, depending on sensitivity and specificity of the test employed, has the potential of false positive or negative tests with the attendant psychosocial costs. Targeted testing is potentially more cost-effective; but, it can be difficult to identify those at high risk. A potential target population is pregnant women with no history of genital herpes and, even more so, female partners of men with a history of recurrent genital vesiculo-ulcerative lesions.

Identification of pregnant women with genital herpes might also lead to a potential intervention that could have an impact on the rate of neonatal herpes.[108] For example, identification of seropositive pregnant women could alert a physician to the possibility of virus shedding at term and, hence, avoid instrumentation at delivery, including the use of scalp electrodes. It could also inform the physician about the possibility of neonatal herpes as a cause of illness within 4 weeks of birth.

The decision to initiate any testing programme should be based on strong evidence that such a programme will do more good than harm.[109] The interventions used to prevent neonatal herpes (e.g. behavioural interventions, condoms, antiviral therapy) are not proven (see page 28) and, thus, it is important that screening should not result in excess, unproven and costly interventions. The only rigorous way to evaluate a testing programme would be a randomized, controlled trial.[109] Such a trial could assess outcomes following testing compared with no screening, the relative impact of the two different approaches, or explore the cost-effectiveness of each strategy.

Potential strategies for the management of the pregnant woman based on type-specific serological testing

A potential management strategy for the pregnant woman may be based on type-specific HSV serology in early pregnancy, with selective partner testing and treatment of the male partner with genital herpes (Figure 1). Here, counselling of the couple is mandatory. If the pregnant woman is HSV seronegative, and her partner is HSV-1 seropositive, they should be counselled on the risks of orogenital contact, and condoms or abstinence should be advocated. If the partner is HSV-2 seropositive, and the pregnant woman is HSV seronegative or HSV-1 seropositive, suppressive antiviral therapy for the male partner may be considered, although proof of its efficacy on transmission awaits the outcome of an ongoing trial of valaciclovir. Condoms and abstinence should be considered. Invasive procedures at delivery should be avoided.

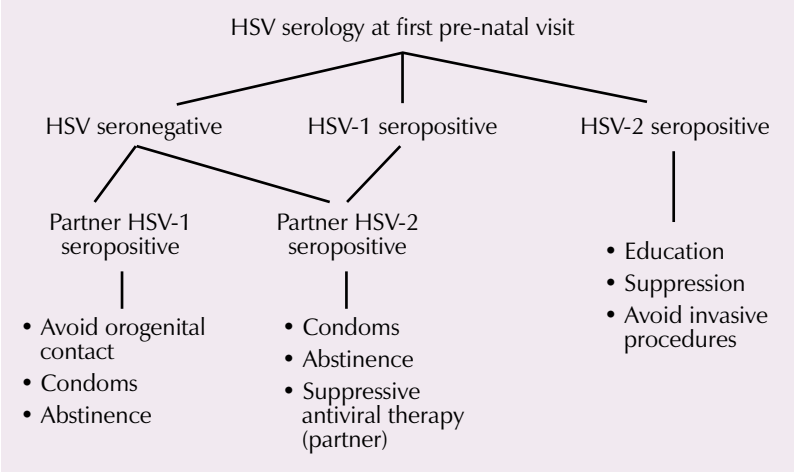

Figure 1: Potential management strategies of the pregnant woman based on type-specific serological testing

Management Approaches for the Pregnant Woman with Genital Herpes

Diagnosis

The diagnosis of genital herpes in the pregnant woman should follow that for the rest of the adult population.

Definitive classification of genital HSV infection during pregnancy as either primary, initial or recurrent, can be accomplished only where clinical evaluation is accompanied by virus culture and type-specific serological testing.

The use of weekly virus cultures in pregnant women with a history of genital herpes is not warranted as it does not predict the neonatal risk of HSV exposure at delivery.

Antiviral treatment in pregnancy

If a woman is pregnant, the potential benefits of treatment should be balanced against potential adverse outcomes for both mother and fetus. All patients should be advised that, in common with the vast majority of drugs, aciclovir, valaciclovir or famciclovir are not specifically licensed for any indication during pregnancy.

Antiviral therapy is not routinely required for genital herpes in pregnancy, although it may be administered for severe primary maternal infection and disseminated disease. Intravenous aciclovir should be initiated in women who have evidence of disseminated infection.

There is insufficient documentation of pregnant women's exposures to aciclovir to draw definitive conclusions on the risks associated with aciclovir during pregnancy, including risks for the fetus.

In one small trial, aciclovir therapy from 36 weeks' gestation has been shown to reduce the number of positive virus cultures, Caesarean sections, recurrences and frequency of virus shedding in women who presented with their first episode at any time during pregnancy. However, the sample sizes of this and other trials are too small for definitive conclusions to be drawn. There have been no trials of antiviral therapy administered at the time of delivery.

Economic modelling of suppressive aciclovir from 36 weeks' gestation indicates that it is cost-effective compared with no therapy or Caesarean section in the management of recurrent genital herpes in pregnancy.

First episode genital herpes during pregnancy

Recommendations

Disseminated or presumed maternal primary HSV infection should be treated with antivirals (*Category 2 recommendation*). Maternal mortality from disseminated HSV infection has been shown to decrease with empirical aciclovir, and the severe or painful symptoms of primary infection may be alleviated with antiviral therapy.

For a woman presenting with a first episode in the third trimester, every effort should be made to characterize it serologically (e.g. primary versus non-primary).

In women with a primary HSV infection after 34 weeks, delivery by elective Caesarean section should be considered (*Category 2 recommendation*).

Recurrent maternal genital herpes during pregnancy

Aciclovir prophylaxis in late pregnancy for women with known recurrences is not currently recommended (*Category 2 recommendation*). However, it may decrease maternal HSV shedding, but, if administered during labour, could load the fetus/neonate with aciclovir with attendant risk for nephrotoxicity. Additional studies are underway and, thus, this recommendation should be reviewed as results become available *(Research need recommendation)*.

Pre-natal type-specific serological testing for maternal HSV infection

Type-specific serological testing for HSV-1 and HSV-2 may have value in the management of the pregnant woman and her partner, although, the impact of serological testing on the rate of acquisition of HSV has not been established. Depending on the local epidemiology and test performance, it has the potential to identify previously infected individuals, those who seroconvert and discordant couples (*Category 1 recommendation*). The results of testing may help guide management of the individual and can provide information to the pregnant woman about her risk of acquiring HSV from her partner, and transmitting HSV infection to her infant. As noted, type-specific serological testing alone will not distinguish genital HSV infection from orolabial HSV infection. The value of serological testing should be assessed in clinical trials together with the benefit of universal or targeted screening of pregnant women.

Management of HSV infection at delivery

Asymptomatic recurrence at delivery has a low (0–3%) risk for resultant neonatal herpes. There are three different management options for women with recurrent HSV who have lesions at delivery:

- Vaginal or Caesarean delivery discussed with the mother who then decides
- Planned vaginal delivery
- Planned Caesarean delivery.

Elective Caesarean section

Caesarean section has the potential to reduce the neonatal exposure to HSV, but evidence for the effectiveness of this intervention is limited and has not been evaluated in controlled trials. Case series studies show that elective Caesarean section is not completely protective for neonatal herpes.

An economic analysis indicates that elective Caesarean section for women with recurrent genital herpes who have lesions at delivery is associated with complications, and substantial financial cost. In comparison, elective Caesarean section for women with first episode genital herpes is cost-saving. However, the model employed is very sensitive to the risk of vertical transmission and the efficacy of Caesarean section.

Mode of delivery: indications for Caesarean section

- In the past, Caesarean section has been used widely but Caesarean section and other management options should be discussed with the patient (*Category 3 recommendation*)
- Controlled trials of management policies to reduce the use of Caesarean section are required (*Research need recommendation*)
- Mode of delivery may be based on clinical findings at the time of delivery (*Category 2 recommendation*). The presence of obvious herpetic lesions is only a relative indication for Caesarean section.

Avoidance of invasive monitoring

Invasive monitoring of the neonate should only be used for defined obstetrical indications (*Category 3 recommendation*). The cases of neonatal herpes averted should be balanced against the possibility of missing some fetal complications (e.g. intrapartum asphyxia).

Strategies to reduce maternal HSV acquisition during pregnancy

There are a number of interventions (e.g. antivirals, condoms, abstinence) that have the potential to limit transmission, but their efficacy should be established.

If the partner has recurrent genital HSV and the woman has no history of genital HSV, sexual abstinence or condom use from week 34 of gestation should be advised (*Category 3 recommendation*).

Potential strategies for screening for HSV infection

There are two potential strategies for identification of pregnant women at risk of HSV infection, targeted and universal (broad) testing. The relative merits of these two approaches should be assessed in clinical trials.

Chapter 3

Management of the Neonate with Herpes Simplex Virus Infection

Diagnosis of Neonatal Herpes: Clinical and Laboratory Findings

Successful management of neonatal herpes relies on a high index of suspicion of herpes simplex virus (HSV) infection and early instigation of therapy. The extent of disease can be assessed using physical evaluation, biochemical tests along with cultures or polymerase chain reaction (PCR) to detect HSV. Thus, an understanding of the presentations of the different categories of neonatal disease[110] can help in management.

The symptoms of infection that should alert the physician to neonatal HSV infection include a progressive febrile illness without bacterial cause, associated with one or more of the following: skin vesicles, seizures, liver dysfunction, coagulopathy or pneumonitis unresponsive to antibiotics.

Skin, eye and mouth lesions

Skin lesions should be carefully sought and examined. However, only approximately one-third of neonates present with cutaneous lesions, whereas one-third develop cutaneous disease later in life and one-third never develop lesions. Moreover, in central nervous system (CNS) disease, 55–60% of cases are devoid of skin lesions at presentation.[33] Even when cutaneous manifestations are present, they may be difficult to detect without careful examination. Thus, diagnostic methods are required.

CNS disease

Infants with CNS disease usually present with fever, and changes in consciousness ranging from lethargy to coma. These changes in sensorium may be followed by focal or generalized seizures that are difficult to control.

Where disease involves only the CNS and is not disseminated, neonatal transmission of HSV to the CNS tends to result in unitemporal involvement with subsequent bitemporal illness as disease progresses.[111]

Typical findings in the cerebrospinal fluid (CSF) include:

- 50–100 white blood cells/mm^3 that are predominantly mononuclear
- Elevated protein concentration.

Disseminated disease

The clinical findings in neonates with disseminated disease include jaundice, bleeding with associated coagulopathy, haemorrhagic pneumonitis, vascular instability, hepatomegaly, hepatitis and neurological deterioration with signs or symptoms of meningitis or encephalitis.

Liver enzymes should also be assessed. If they are progressively abnormal, the index of suspicion for disseminated neonatal herpes is increased, especially in the first week of life.

Diagnostic Methods

As the initial symptoms of neonatal herpes are non-specific and lesions may be absent or not obvious, other diagnoses are often proposed (e.g. sepsis) and this can lead to a delay of several days before initiating appropriate therapy. The high risk of death or neurological damage with delayed or no treatment of neonatal infection requires that diagnosis be pursued promptly whenever an infection is suspected and empiric treatment with intravenous aciclovir initiated at the time diagnostic tests are ordered. There is, therefore, a need for

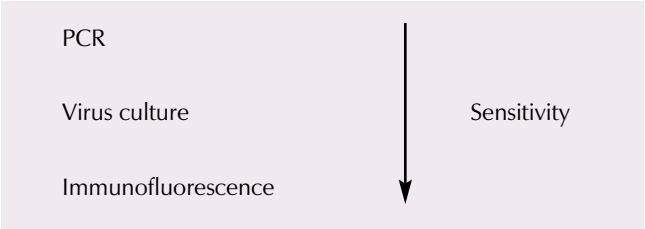

Figure 1: Sensitivity of diagnostic tests for neonatal HSV infection

accurate and rapid diagnostic methods to help reduce the mortality and incidence of serious neurological sequelae in surviving children. However, the available tests vary in their sensitivity (Figure 1).

The importance of obtaining evidence of infection suggests that specimens should be collected and tested as early as possible. Caution is advised as a positive culture result for samples obtained from the skin immediately after delivery may represent infant contamination (i.e. transient colonization from mother to infant during birth) rather than true neonatal infection. Taking samples at 36–48 hours may reduce the chances of a false-positive diagnosis, but a delay in diagnosis should be balanced against any delay in initiating treatment.

Culture

The current standard for diagnosis of neonatal HSV infection is virus culture. About 80% of cultures produce a visible cytopathic effect within 2 days and 99% by 4 days.[112] In contrast to the relatively high sensitivity of viral cultures of mucocutaneous lesions, fewer than 20% of newborns with CNS disease have positive virus cultures of the CSF.[92]

PCR

PCR has contributed greatly to the rapid diagnosis of neonatal HSV infection, particularly HSV infections in the CNS. In addition to being more sensitive than virus culture, it avoids many of the problems associated with culture methods, such as inadequate quantity of specimen, bacterial contamination and inactivation of virus by suboptimal handling. Where performed by an experienced laboratory, PCR is highly sensitive and specific. It is, therefore, important that there is stringent quality control at the testing laboratory, and to document the sensitivity and specificity of the assay.

PCR Analysis of the CSF

PCR is a highly sensitive and specific assay for the diagnosis of HSV infection of the CNS. In patients with biopsy-proven herpes simplex encephalitis, PCR of the CSF had a sensitivity of 98% and a specificity at 94%.[113] Other studies, in which diagnosis of HSV encephalitis was based on criteria other than isolation of HSV from brain tissue, have reported that PCR of the CSF is also highly sensitive and specific.[114] In neonatal herpes encephalitis, the sensitivity for demonstration of HSV DNA in CSF has been reported to range from 71% to 100%.[115–119]Accordingly, the sensitivity of PCR is often considered to be lower in neonatal herpes CNS disease than in adults.[118] However, the majority of infants in this neonatal herpes study were receiving treatment. Antiviral treatment lowers the HSV DNA concentration in the CSF; in one study after 1 week of therapy, only 80% of CSF samples were PCR positive for HSV DNA.[116] Consequently, it is difficult to make meaningful determination of the sensitivity of a technique where patients are receiving treatment.

A retrospective analysis of CSF specimens from 77 neonates enrolled in a comparative trial of aciclovir and vidarabine validated the use of PCR in the management of infected infants.[116] The infants were classified as having SEM, CNS or disseminated disease, and CSF samples were analysed for HSV DNA (Table 1). In this study, HSV DNA was detected in the CSF of 24% of infants with presumed SEM disease suggesting that HSV can infect the CNS without symptoms.[116] The significance of this finding, and the implications of a positive PCR result in infants with no evidence of CNS involvement, requires further prospective study.

PCR analysis of the CSF for HSV DNA should be used to diagnose neonatal herpes. However, its application should be investigated further. The technique may also help to predict therapeutic outcome. In addition, PCR can use samples from different sites, although their diagnostic utility needs to be determined fully.

PCR result for CSF	Disease classification		
	SEM ($n=29$)	CNS ($n=34$)	Disseminated ($n=14$)
Positive	7 (24%)	26 (76%)	13 (93%)
Negative	22 (76%)	8 (24%)*	1 (7%)

**On treatment for an average of 10 days*
SEM: skin, eye and mouth

Table 1: PCR results of HSV DNA detection in CSF in neonatal herpes[116]

Potential PCR-based diagnostic methods

PCR analysis of the peripheral blood mononuclear cells (PBMC) and plasma may be a useful diagnostic tool in neonatal herpes.[120] In a series of 11 consecutive cases of neonatal HSV infection, PCR was performed in specimens from at least one site. HSV DNA was detected in the PBMC of 60% (six of 10) of infants tested, in the plasma of 67% (four of six tested) and the CSF of 36% (four of 11 tested). These data suggest that HSV viraemia is more frequent than previously appreciated and PCR of plasma and PBMC could be used to establish a diagnosis of HSV infection earlier.[120]

Preliminary results indicate that PCR to detect HSV DNA in dried blood spots on Guthrie cards is useful for retrospective diagnosis of neonatal HSV infection.[121] Guthrie cards from four infants with suspected neonatal herpes and 73 controls were analysed by PCR. Three of the four suspected cases were positive for HSV-2 DNA and one was positive for HSV-1 DNA; of the controls, two were HSV-1 DNA positive whereas the remainder were HSV-1 and HSV-2 DNA negative. Thus the sensitivity of this test was 100% and the specificity was 97%.[121] In considering this test, strict procedures are needed to monitor potential cross-contamination from adjacent Guthrie cards.

Direct immunofluorescence

Antigen detection of HSV in skin lesions by direct immunofluorescence is the least sensitive technique (sensitivity of 41–70% compared with culture),[122–125] but it has the advantage that, if lesion scrapings are used, a diagnosis can be made within hours. In general, as the amount of diagnostic material is often limited, culture (and/or PCR) should be used in preference to this technique. Moreover, many neonates have no visible lesions. Where there are multiple skin lesions and samples have already been obtained for culture (or PCR), it is reasonable to carry out direct immunofluorescence if there are remaining vesicles to sample.

Treatment

Aciclovir and vidarabine have been shown to reduce the morbidity and mortality of HSV infection in the neonate.[4,126,127] A study comparing aciclovir (10 mg/kg every 8 hours for 12 days) with vidarabine (10 mg/kg/ every 8 hours for 12 days) demonstrated that both drugs reduced overall mortality from SEM, disseminated disease or encephalitis to approximately 19% and reduced morbidity.[4] In comparison, the mortality rate of untreated neonatal herpes is high for infants with disseminated disease (90%) and CNS disease (50%).[32,62,63] For both treatments, the outcome varied according to the extent of disease; no infants with SEM disease died whereas the mortality rate was 14% in CNS disease and over 50% in neonates with disseminated disease (see Figure 2).[4]

The morbidity for all treatment groups showed no statistical difference when comparing vidarabine and aciclovir (Figure 2). Of the infants who survived, on average, development was normal in 95% of those with SEM involvement, 45% of those with CNS disease and in 65% of those with disseminated manifestations. In addition, the proportion of children returning to normal function was significantly greater than in earlier trials, which may reflect

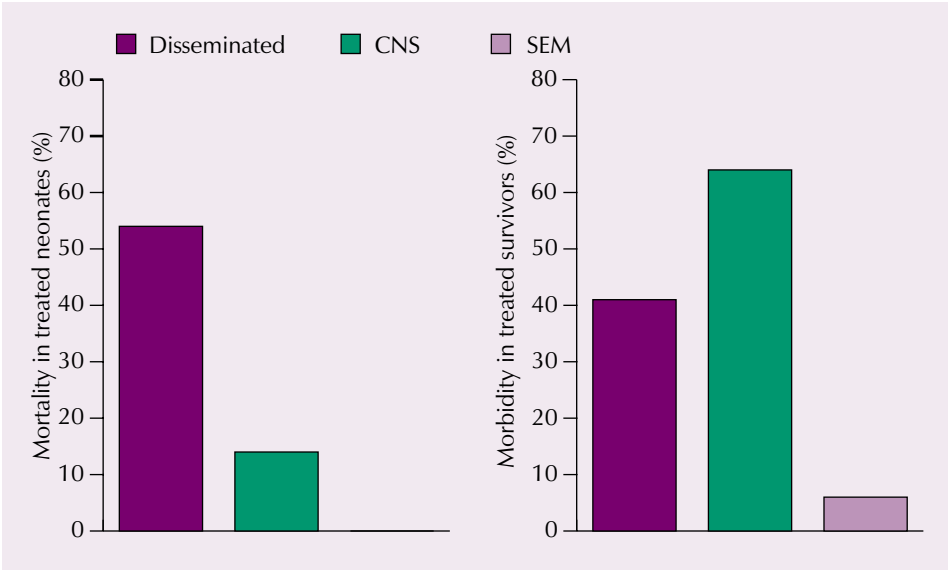

Figure 2: Morbidity and mortality in neonatal herpes for which treatment was indicated after a mean of 4 days disease[4]

the prevention of disease progression with early therapy. In the study, the mean duration of disease for all children before therapy was administered was 4 days and, thus, there is the opportunity for even earlier intervention.

In practice, aciclovir is used because of its safety profile and convenient dosage regimen compared with vidarabine.[4] Preliminary results from an ongoing study indicate that increasing the aciclovir dose to 60 mg/kg/day (20 mg/kg every 8 hours) for 21 days reduces morbidity and mortality in infants with CNS or disseminated disease compared with historic controls (Table 2).[128] The only adverse event judged to be treatment-related was neutropaenia (absolute neutrophil count <1000) which occurred in 14 (19%) of 74 infants receiving the higher dose of aciclovir. The neutropaenia resolved either spontaneously or soon after the 21 days of treatment.[128]

	Mortality at 12 months of age		Surviving infants developing normally after 12 months follow-up	
	Aciclovir 30 mg/kg/day†	Aciclovir 60 mg/kg/day	Aciclovir 30 mg/kg/day†	Aciclovir 60 mg/kg/day
CNS disease	14% (*n*=35)	4% (*n*=24)	29% (*n*=28)	31% (*n*=13)
Disseminated disease	61% (*n*=18)	30% (*n*=33)	60% (*n*=5)	79% (*n*=19)

†*Historic controls*

Table 2: Mortality and normal development in survivors in infants with CNS or disseminated HSV infection treated with aciclovir 60 mg/kg/day[128]

Monitoring treatment of neonatal HSV infection

An analysis of CSF specimens from the neonates enrolled in the comparative trial of aciclovir and vidarabine discussed above found that one of the seven SEM infants with HSV DNA in the CSF developed severe neurological impairment within 1 year of cessation of intravenous antiviral therapy.[116] This suggests that detection of HSV DNA in the CSF may have clinical relevance. Moreover, infants who had HSV DNA detected in the CSF following completion of antiviral therapy were more likely to die or suffer serious neurological impairment than those whose post-therapy CSF specimens were PCR negative (Table 3).[130] It should be noted that the limitations of this study (e.g. possible sampling bias; differences in disease classification

Infant characteristic	PCR result		
	Negative (%)	Positive (%)	*P* value
Disease classification			
CNS	4 (36.4)	14 (73.7)	<0.001
Disseminated	0 (0.0)	5 (26.3)	
SEM	7 (63.6)	0 (0.0)	
CSF indices			
Normal	6 (54.5)	1 (5.3)	
Abnormal	3 (27.3)	17 (89.4)	
Morbidity and mortality after 12 months			
Normal	6 (54.5)	1 (5.3)	<0.001
Mild	0 (0.0)	0 (0.0)	
Moderate	1 (9.1)	3 (15.8)	
Severe	2 (18.2)	10 (52.6)	
Non-survival	0 (0.0)	5 (26.3)	
Unknown	2 (18.2)	0 (0.0)	

Table 3: PCR results of HSV DNA detection in CSF in infants with neonatal herpes following completion of antiviral therapy[130]

between PCR-negative and PCR-positive groups) make it difficult to draw definitive conclusions.[116] Another study found that the persistence of HSV DNA in the CSF after the end of intravenous aciclovir treatment was associated with a poor prognosis.[118] This persistence of virus may reflect the inability of the host to control the infection despite antiviral therapy.

It is likely that the HSV DNA copy number in an individual during or after treatment is a marker of therapeutic effect. Recent data suggest that the initial CSF titre of HSV DNA determined by quantitative PCR is prognostic in adults; concentrations of more than 100 copies/ml correlated with both reduced level of consciousness at presentation and with likelihood of future neurological impairment.[129] Quantitative PCR testing of serial CSF samples may also help to monitor the progress of treatment of neonatal HSV infection and may be used as a prognostic tool. With aciclovir, quantitative PCR detected lowered HSV copy number in the CSF of five neonates although the study did not relate the outcome to the reduction in HSV DNA.[115] In a neonatal herpes treatment study, PCR testing of serial CSF samples revealed that a rapid decrease in virus load to a non-detectable level after a 14-day course of drug therapy (20 mg/kg every 8 hours) was associated with a significantly lower likelihood of serious neurological impairment than if the virus remained detectable. Infants who retained some virus burden were at high risk of developing CNS disease and substantial neurological impairment.[128]

Cost-effectiveness of antiviral therapy for neonatal herpes

There are little data on cost-effectiveness of treatment of neonatal herpes. In one analysis antiviral therapy for neonatal herpes has been shown cost-effective compared with no treatment.[131] Information on disease occurrence and survival was based on data from therapeutic trials and historical reviews. In the analysis, treatment approaches for any form of the disease were considered and compared with no treatment. The elements measured included direct medical costs, institutional care and special education, and were valued at 1995 levels.

The analysis revealed that treating neonatal herpes with antiviral therapy can reduce societal costs and save lives where the disease is of the SEM form.[131] Where the disease has progressed to the more serious CNS and disseminated multiorgan forms, antiviral therapy involves incremental societal costs per additional life saved (Table 4).

The finding that treating SEM disease is more cost-effective than treating CNS disease or disseminated disease reflects the probability of a normal outcome being higher where SEM

Strategy	Cost (US$)	Marginal cost (US$)	Life years saved	Marginal lives saved	Cost per life year saved (US$)	Marginal cost (US$)/ Marginal lives saved
SEM						
No drug	98 474	78 601	1.1	–0.8	90 444	
Drug	19 873		1.9		10 467	Cost saving
CNS						
No drug	120 859		0.7		167 336	
Drug	172 808	51 950	1.4	0.7	122 233	75 125
Disseminated						
No drug	69 054		0.4		173 045	
Drug	86 714	17 660	0.8	0.4	111 476	46 619

Table 4: Marginal cost per additional life year saved in neonates treated and not treated with antiviral therapy[131]

disease is treated than for either CNS or disseminated disease. Thus, a much larger gain occurs where the SEM case is treated, whereas antiviral drug treatment of the more serious manifestations produces a gain in lives saved, but only at a greater expense to society. Notably, antiviral therapy compares favourably with many other healthcare interventions (e.g. a cost per life year saved of US$24 305 for respiratory syncytial virus infection).[131]

Suppressive antiviral therapy in neonatal herpes

The value of suppressive therapy (long-term therapy to control recurrent HSV reactivation) in neonatal herpes has not yet been established. Suppressive oral aciclovir (300 mg/m^2 twice daily or three times daily) was administered for 6 months to 26 neonates aged 1 month or younger who had virologically confirmed SEM disease.[132] Antiviral therapy prevented cutaneous recurrences of HSV-2 after SEM disease in 13 of 16 (83%) children, seven of these 16 infants experienced recurrences following cessation of the drug.

Of note, 12 of 26 in the suppressive phase of the study developed neutropaenia (<1000 cells/mm^3) that resolved without dosage alteration in ten children, with dosage adjustment in one child and after withdrawal of therapy in the remaining infant.[132] Further, in one infant, HSV DNA was detected in the CSF during a cutaneous recurrence, and an aciclovir-resistant HSV mutant was isolated from another patient during the course of the study.[132]

In conclusion, oral aciclovir prevented cutaneous recurrences of HSV-2 following neonatal herpes in this small trial. The effect of such therapy on cutaneous recurrences and on neurological outcome should be assessed in larger studies before routine use of suppressive therapy can be recommended. A clinical trial is being initiated that will evaluate the efficacy of long-term suppressive therapy with oral aciclovir in infants with CNS disease with or without evidence of dissemination to other organs.

Management of Suspected or Proven Neonatal HSV Infection

There are four clinical scenarios that must be considered for the infant born to a woman with genital HSV infection:

- Infant born to mother with clinically apparent first episode genital herpes at delivery
- Infant born to a mother with clinically apparent recurrent genital herpes at delivery

- Infant born to mother with a history of genital herpes but no obvious lesions at delivery
- Infant with clinical presentation compatible with neonatal HSV infection.

For the first three scenarios, the history and presentation of a woman with genital HSV infection at delivery influences the likelihood of neonatal herpes and, therefore, the approach to diagnosis and treatment. For the newborn with a clinical presentation compatible with neonatal herpes, immediate treatment with intravenous aciclovir and prompt diagnosis are mandatory. In all four clinical scenarios, the approach to diagnosis and treatment is the same when neonatal HSV infection is suspected.

Diagnosis

The high risk of death or neurological damage with delayed, or no treatment, of neonatal HSV infection requires that diagnosis be pursued promptly if the infection is suspected. At the same time that diagnostic tests are ordered, empiric treatment with intravenous aciclovir must be initiated.

Ideally, a paediatrician experienced at identifying the signs of neonatal herpes should examine the infant. It is not sufficient to rely solely on the presence of skin lesions for diagnosis as neonatal herpes can occur in their absence. Therefore, diagnostic methods are required whenever neonatal HSV infection is suspected. Material should be collected from **all** the following sites and submitted to the laboratory for virus culture and/or PCR detection of HSV:

- Skin or mucosal lesions
- Conjunctiva
- Mouth and throat
- Rectum
- Urine
- CSF.

Evidence of disseminated or CNS infection should be sought by performing liver function tests, complete blood cell count (CBC), CSF analysis and, if there are any respiratory abnormalities, a chest X-ray. Whenever possible, PCR analysis of the CSF for HSV DNA should be used to diagnose suspected neonatal herpes; a finding of HSV DNA in the CSF is evidence of disseminated or CNS infection.

Treatment

Intravenous aciclovir (20 mg/kg every 8 hours) is recommended for suspected or proven neonatal HSV infection (*Category 2 recommendation*). Early therapy, which may improve long-term neurological outcome, is vital and, therefore, treatment should be started at the time diagnostic tests are ordered.

The duration of the intravenous aciclovir treatment depends on whether or not neonatal herpes is localized. If the disease is limited to the skin, eyes or mouth (i.e. normal CSF), the treatment should be for 14 days. For other forms of neonatal HSV infection (i.e. abnormal CSF), administration for 21 days is recommended. If a CSF analysis is not available, the longer treatment period should be used.

In no circumstances should oral or topical therapy be used to treat neonatal HSV infection.

Given this common approach to diagnosis and treatment when neonatal HSV infection is suspected, the differences in management for each of the clinical scenarios are provided below.

Infant born to a mother with clinically apparent first episode genital herpes at delivery

Specimens (but not a CSF sample) for virological assays should be obtained from the infant at delivery, rather than 36–48 hours postpartum, because of the importance of rapid diagnosis. Prophylactic intravenous aciclovir therapy at 60 mg/kg/day in three divided doses for 14 days is recommended. If disease develops, a work-up of the central nervous system is indicated, including CSF examination by PCR. The infant should be treated with intravenous aciclovir therapy at 60 mg/kg/day in three divided doses for 21 days if there is evidence of disseminated or CNS infection.

Infant born to a mother with clinically apparent recurrent genital herpes at delivery

The parents should be educated about the signs of the disease. Prophylactic therapy is not appropriate because the risk of HSV transmission to the infant is low and the risk of developing disease is very small.

Infant born to mother with a history of genital herpes but no obvious lesions at delivery

In this setting, parents should be educated about the signs of disease. As above, prophylactic therapy is not appropriate.

Infant with clinical presentation compatible with neonatal HSV infection

Specimens for virological assays (e.g. culture, PCR) should be obtained from the infant at delivery and a work-up of the CNS that includes CSF examination by PCR is indicated. As for all other scenarios, empiric treatment with intravenous aciclovir must be started immediately (at the time diagnostic tests are ordered).

Reducing the Delay between Onset of Symptoms and Treatment Initiation

The average delay between onset of neonatal herpes symptoms and hospital admission is 4 days.[4,36] A number of factors contribute to this delay; one is that although the delivering obstetrician may be aware of maternal genital herpes, the physician assessing the symptomatic infant often is not. Additionally, parents may not understand the risks of vertical transmission and therefore may not seek medical advice when the child first becomes ill. The situation is complicated further because the signs and symptoms of neonatal herpes can be non-specific and usually develop after the infant has been taken home.[36]

Educating parents with known genital herpes about risks to the child is one way to increase the possibility of earlier diagnosis. They should be familiarized with the signs and symptoms of neonatal herpes infection, and should receive explicit instructions as to when and how to seek medical attention for their newborn.

Further Considerations in the Management of the Infant with Neonatal Herpes

Acute management

In addition to the administration of antiviral therapy, there are other considerations in the acute management of the infant with neonatal herpes (Table 5).

Long-term management

Long-term follow-up of infants with neonatal herpes should be instituted to monitor sequelae. The evaluations, which should be conducted on an annual basis, include:

- Neurodevelopmental assessments
- Ophthalmological evaluations
- Hearing assessments.

Management of cutaneous recurrences of neonatal herpes

Management of the cutaneous recurrences in infants with SEM is a contentious issue. Suppressive antiviral therapy may reduce the risk of neurological impairment and a trial is underway to test this hypothesis. The benefit of suppressive antiviral therapy has yet to be established; episodic therapy may also have a role in managing cutaneous recurrences.

- Maintenance of fluid and electrolyte balance
- Management of shock
- Management of disseminated intravascular coagulation
- Control of seizures
- Respiratory support
- Antimicrobial therapy for concomitant bacterial infections

Table 5: Additional considerations in the acute management of the infant with neonatal herpes

Impact of Neonatal Herpes on the Family

Neonatal herpes can have a major impact not only on the infected infant but also on siblings and parents. There can be substantial stress caused by concern about an infant with a potentially life-threatening infection, and this may be exacerbated by guilt about transmission of a sexual pathogen. The emotional, physical and financial burden of the long-term care for a neurologically impaired child can be very high and the sequelae, which can be widespread, include divorce and behavioural problems with siblings. Family counselling interventions may help reduce the effects of neonatal herpes although their success should be evaluated.

Counselling the Pregnant Woman with a Diagnosis of Genital Herpes or with a Child who has Neonatal Herpes

The requirements of counselling

Counselling should be client-centred, providing for each individual's needs. It should be a participatory process that facilitates the client's insights, confidence and skills to help them make informed decisions. To this end, a critical principle of counselling is listening. Another important element is to have no agenda for an outcome as this could impart the counsellor's views rather than addressing the needs of the client.

An important principle of counselling is to share information and be honest. Clients who find that they have been misinformed, or not fully informed, may lose confidence in their healthcare provider. Another vital aspect is to address the implications as well as the clinical facts of the disease and to discuss the possible outcomes of a suggested intervention, or lack of one, with the client. This will allow the client to reach an informed decision about the available options. This can be a challenge to the counsellor who must assist each client to see the full spectrum of issues, and help to facilitate the decision-making. In all these contexts, it is vital to 'translate' the medical terminology and thereby minimize barriers to understanding.

Of all the aspects of counselling, one of the most important principles is to provide follow-up resources. This may be a psychologist, websites (e.g. **www.herpesweb.net**), or support groups. The provision of follow-up resources is necessary as the client may have issues and questions that develop with time.

Challenges to effective counselling

Stigma

The stigma associated with a diagnosis of herpes makes counselling difficult. In a qualitative survey of telephone calls to the *American Social Health Association* (ASHA), a number of common concerns arose, which included:

- 'I have herpes, can I have an infant?'
- 'I have herpes. Will everyone know this when I have an infant?'
- 'I want to become pregnant, but I am afraid to tell my doctor that I have herpes, is that OK?'

These questions allude to the shame and embarrassment associated with genital herpes, as well as to uncertainties about the effect of genital herpes during pregnancy and on the unborn child. Even in those who seem to have adjusted to their diagnosis, stigma is still harboured.

Guilt

The guilt associated with the transmission of 'genital herpes' to the neonate can be reduced by destigmatizing genital herpes and placing the risk of neonatal herpes in context.

Other considerations

When counselling, the woman may be willing to undergo personal risk, such as the risks associated with elective Caesarean section, to avoid harming her child (this is not unique to genital herpes).

Status issues

There are issues of status (power) in counselling, some of which are the result of the physician/counsellor–patient relationship and whereas others are the consequence of physical factors. Power differences may be addressed by recognizing the perception of a difference in status between physician and patient. Similarly, differences in gender, race and education should be acknowledged and mimimized. It is also important to provide an environment in which people feel comfortable, such as a quiet office, and not talking across a table or chair, to minimize any power differences.

Time constraints

One of the major barriers to effective counselling by the healthcare provider is lack of time and provision of in-depth counselling may be unrealistic. Thus, a paradigm may be that the provider makes the diagnosis and has an initial discussion with the client who is then referred to a counsellor. The decision as to who provides and delivers counselling (e.g. practice nurse, counsellor at an STD clinic) will depend on the preferences of the physician and the healthcare system in which they operate.

Research Needs

It is important to reassess continually the natural history of neonatal herpes. Other aspects that should be evaluated prospectively include:

- PCR detection of HSV DNA in CSF and blood
- Family counselling
- The value of suppressive antiviral therapy – controlled trials are in progress.

A vaccine that could prevent neonatal herpes is desirable.

Summary

Management of the neonate with possible HSV infection

Diagnosis

The high risk of death or neurological damage with delayed or no treatment of neonatal HSV infection requires that diagnosis be pursued promptly whenever the infection is suspected and that empiric treatment with intravenous aciclovir be initiated at the time diagnostic tests are ordered.

Neonatal herpes may occur in the absence of skin lesions and, thus, diagnostic methods are required. Whenever neonatal HSV infection is suspected, material from skin or mucosal lesions, conjunctival swabs, mouth swabs, rectal swabs, urine and CSF should be submitted to the laboratory for virus culture and/or PCR detection of HSV (*Category 1 recommendation*).

Evidence of disseminated or CNS infection should be sought by performing liver function tests, CBC, CSF analysis and, if there are any respiratory abnormalities, a chest X-ray (*Category 1 recommendation*). PCR analysis of the CSF for HSV DNA should be used to diagnose suspected neonatal herpes (*Category 2 recommendation*).

Treatment

Intravenous aciclovir (20 mg/kg every 8 hours) is recommended for neonatal HSV infection (*Category 2 recommendation*). Early therapy, which may improve long-term neurological outcome, is recommended (*Category 1 recommendation*). The duration of intravenous aciclovir (20 mg/kg every 8 hours) treatment should be 14 days for disease that is limited to the skin, eyes or mouth (i.e. normal CSF), and 21 days for other forms of neonatal HSV infection (i.e. abnormal CSF) (*Category 1/2 recommendation*). This recommendation applies to each of the clinical scenarios outlined in Table 6.

In no circumstances should oral or topical therapy be used to treat neonatal HSV infection (*Category 1 recommendation*).

The value of suppressive antiviral therapy for prevention of recurrences after the initial treatment of neonatal HSV infection has not been established (*Category 2 recommendation*). A preliminary trial demonstrated that oral aciclovir (300 mg/m^2 three times daily) prevented HSV recurrences after SEM disease but was associated with reversible neutropaenia in 46% of infants.

Monitoring treatment of neonatal herpes simplex virus infection

Infants in whom there is persistence of HSV DNA in the CSF following completion of antiviral therapy are more likely to die or suffer serious neurological impairment than infants whose post-therapy CSF specimens are PCR negative (*Category 3 recommendation*).

Quantitative PCR testing of serial CSF samples may also help monitor progress and be useful as a prognostic tool (*Research need recommendation*).

Potential diagnostic methods

PCR of peripheral blood mononuclear cells and plasma may be a useful diagnostic tool (*Research need recommendation*).

PCR to detect HSV DNA in dried blood spots on Guthrie cards may be useful for retrospective detection of HSV infection (*Research need recommendation*).

Impact of neonatal herpes on the family

Neonatal herpes is a cause of substantial stress to the family. This may be due to concern about a potentially life-threatening infection, and may be exacerbated by the guilt about the transmission of 'genital herpes'. Also it may be caused by the need for long-term care of the neurologically impaired child and the associated medical expense. The impact of neonatal infection may extend to divorce and behavioural problems with other siblings. Because of the severe psychosocial sequelae of neonatal herpes, family education and counselling are mandatory.

Infant born to mother with, at delivery	Diagnosis				Treatment	
	Paediatrician to examine infant	Collect specimens for virology studies **at delivery**	If signs of neonatal HSV infection, collect specimens **including CSF** for virology studies	Inform parents about disease	Prophylactic iv aciclovir	Commence empiric iv aciclovir If CSF normal – 14 days If CSF abnormal – 21 days If CSF not obtainable – 21 days
Clinically apparent first episode genital herpes	Yes	Yes (**not CSF**)	Yes	Yes	Yes	Yes
Clinically apparent recurrent genital herpes	Yes	No	Yes	Yes	No	Yes
History of genital herpes but no obvious lesions	Yes	No	Yes	Yes	No	Yes
Infant with clinical presentation compatible with neonatal HSV infection	Yes	Yes (**include CSF**)	–	Yes	–	Yes

Table 6: Treatment recommendations for neonatal herpes

Counselling

The principles of counselling are to:

- Listen
- Have no agenda for outcome
- Be honest:
  - do not withhold information
  - 'translate' medical jargon
  - be pragmatic about the disease
- Discuss outcome possibilities
- Provide follow-up resources.

There are several issues which can make counselling difficult. A major obstacle is the guilt and stigma associated with herpes. These can be reduced by pragmatic discussion of the infection and its consequences. Status differences between the counsellor and client (e.g. gender, race, education) may also hamper the counselling process; these should be recognized and their influence minimized.

Another barrier to effective counselling is lack of time. An approach may be for the healthcare provider to make the diagnosis and have initial consultations with the patient before referral to a counsellor. The counsellor may be in the physician's practice or at a separate institution.

Priorities for research

It is important to evaluate prospectively:

- PCR detection of HSV DNA in the CSF and blood to diagnose neonatal herpes and assess response to treatment
- The overall benefit of family counselling.

Controlled trials of suppressive therapy to prevent HSV recurrences after neonatal herpes are in progress.

A vaccine to prevent neonatal herpes is desirable.

Epidemiology and Natural History of Congenital and Perinatal Cytomegalovirus Infection

Introduction

Cytomegalovirus (CMV) is an important cause of perinatal and congenital morbidity and mortality. Congenital infection occurs through transplacental transfer of the virus from mother to fetus whereas contact of the newborn in the immediate post-natal period produces perinatal infection. Primary sources for such perinatal infections include breast milk as well as transfusion-associated passage of infected white blood cells. The two types of neonatal infection, which differ in both their epidemiology and impact on the neonate, are discussed below.

Epidemiology of Congenital CMV Infection

CMV is the leading cause of congenital virus infection in the world. Approximately 1% of all infants are congenitally infected with CMV, with the prevalence of infection ranging from 0.2% to 2.2%.[133] In comparison, approximately 1–15% of infants are perinatally and post-natally infected with CMV by 6 months in the USA.[134]

By the end of their first year, 10–40% of children excrete virus in urine with the actual rate depending on maternal seropositivity and breast-feeding practice.[135,136] Children with CMV infection can shed CMV in their urine and saliva for many years.[135]

Evidence for the source of CMV comes from case reports, seroepidemiological studies and molecular-epidemiological studies.[137] In most of these studies, the CMV source was a young child and acquisition rates of 43–53% have been observed.[137] In the USA, an increased risk of transmission has been shown for women working at day care centres, nursery schools or pre-schools who care for young children.[138] The annual rate of CMV acquisition in women who work in such environments range from 8% to 20% as compared with 3–5% in the general population.[138–142] In comparison, there is no increased risk of congenital CMV infection for women working in the healthcare profession.[137]

In the UK, a prospective study in London demonstrated that child-to-mother transmission of CMV plays a significant part in the acquisition of CMV infection in adult life.[143] Sexual activity is also an important source of maternal CMV infection in epidemiological studies conducted in the USA.[144,145]

In adolescents and young adults, the persistence of CMV in saliva, cervical secretions and semen indicates that infection may be spread through kissing and sexual contact.[146] A less common source of infection is blood product transfusion.

Sociodemographic factors, such as urban residence, ethnic origin and socioeconomic status, also affect the rate of CMV acquisition. In the UK and USA, 40–60% of adults in middle to upper socioeconomic strata are CMV seropositive compared with 80% or greater of adults of lower socioeconomic status.[134,147,148] Higher rates of CMV seropositivity are evident in developing countries, with 80% of 3-year-old children and most adults being infected with CMV.[149–151]

Mechanism of Infection

It is thought that CMV is transmitted to the fetus via cytotrophoblast cells that are infected by maternal leucocytes.[152,153] However, there may be other routes of virus transmission. Even if *in vitro* data do not substantiate transplacental migration of infected white blood cells, it is possible that the virus may first infect placental tissues and later amniotic cells.[154]

Consequently, infected amniotic cells would be ingested by the fetus, after which the virus could replicate in the oropharynx and invade the fetal circulation to reach target organs, including the central nervous system (CNS), liver, inner ear, bone marrow, kidney, adrenals, and ductal epithelium and vascular endothelium in many sites.

Timing of maternal infection

Transmission of CMV from mother to fetus is assumed to occur during all three trimesters with equal frequency and occurs by transplacental passage of the virus after maternal viraemia.[147,148,155] Severe adverse neurological outcome following primary infection in pregnancy is greater when the infection occurs before 27 weeks' gestation although studies that conclusively demonstrate this risk have not been conducted.[147,148,155–157]

Factors Influencing *In Utero* Transmission of CMV

Several factors influence the transmission of CMV infection to the fetus and the consequences of fetal infection. The major ones are:

- Primary versus recurrent infection
- CMV-specific antibody response
- Maternal age.

Primary versus recurrent infection

Primary infection with CMV occurs in 0.7–4.1% of pregnancies, with a mean reported transmission rate to the fetus of 40% (reported range 24–75%).[134,147,155,157–159] CMV is unusual among viruses causing congenital infections in that it can be transmitted from mother to fetus during both a primary infection and a recurrence. In contrast to the high transmission rate in primary infection, the transmission rate during recurrent infection is much lower (1–2.2%).[134,160] A prospective study of women known to be seropositive before conception recorded an incidence of congenital infection of 1.9% (Table 1), which was similar to the 2.2% rate of congenital CMV infection reported in the general infant population.[134]

	Total	No. infected (%)
General infant population	1412	31 (2.2)
Documented recurrent maternal infection	541	10 (1.9)

Table 1: Incidence of congenital CMV infection in a low income population[134]

The intra-uterine transmission in the presence of substantial humoral immunity has been attributed to reactivation[134] as well as infection with exogenous virus.

Evidence of the importance of CMV reactivation comes from epidemiological studies of congenital CMV. These have shown a direct relationship between its incidence and the rate of maternal seropositivity (Table 2). A partial explanation for this phenomenon is the observation that the virus can be transmitted from the mother to the fetus by reactivation of a latent infection, even when the woman is known to have been infected months or years before conception.[134]

Although, it is thought that reactivation is a more important cause of intra-uterine transmission than infection with exogenous virus, this must be confirmed in large-scale studies.[161]

CMV-specific antibody response

There are differences in CMV-specific antibody responses between women who transmit the virus to their offspring and those who do not.[162] Women with CMV disease, and those with subclinical infection and intra-uterine transmission, have a more prolonged and enhanced serum antibody response compared with those who do not transmit CMV *in utero*.[163,164] The properties of the antibody response to glycoprotein B (gB) have been determined in a study of 58 women with primary CMV infection during pregnancy. It characterized differences

Country	Congenital CMV infection (%)	Maternal seropositivity (%)
England (Manchester)	0.24	25
Denmark (Aarhus-Viberg)	0.4	52
Canada (Hamilton)	0.42	44
Canada (Halifax)	0.55	37
USA (Alabama)	0.6	60
USA (Texas)	0.6	50
England (London)	0.69	58
USA (Texas)	1.2	83
Ivory Coast	1.38	100
Japan (Sendai)	1.4	83
Chile (Santiago)	1.7	98
Finland (Helsinki)	2.0	85
USA (Alabama)	2.2	85

Table 2: Incidence of congenital CMV infection according to the rate of maternal immunity in different studies[134]

between seropositive women who transmit CMV infection *in utero* (transmitters) and those who do not (non-transmitters).[162] Glycoprotein B is a major envelope glycoprotein of CMV and is the major target of the anti-envelope antibody response and virus neutralizing activity.

In this study of maternal antibody response, the anti-gB Immunoglobulin (Ig) G antibody titre was significantly higher ($P<0.05$) in transmitters than non-transmitters (Figure 1).[162] In addition, the IgM response to CMV was also significantly higher in transmitters than non-transmitters ($P<0.05$), (Figure 1). This suggests that the amount of antibody does not reflect protection from transmission,[162–164] a finding which has also been reported in a study of HIV-infected patients with retinitis.[165] Possibly, the higher antibody levels in the transmitters reflect higher levels of virus replication or more prolonged replication.

Women who do or do not transmit CMV can also be differentiated based on their neutralizing antibody titre. Lower titres are present in transmitters versus non-transmitters (Figure 2), suggesting an association between neutralizing antibodies and intra-uterine transmission.[162,166]

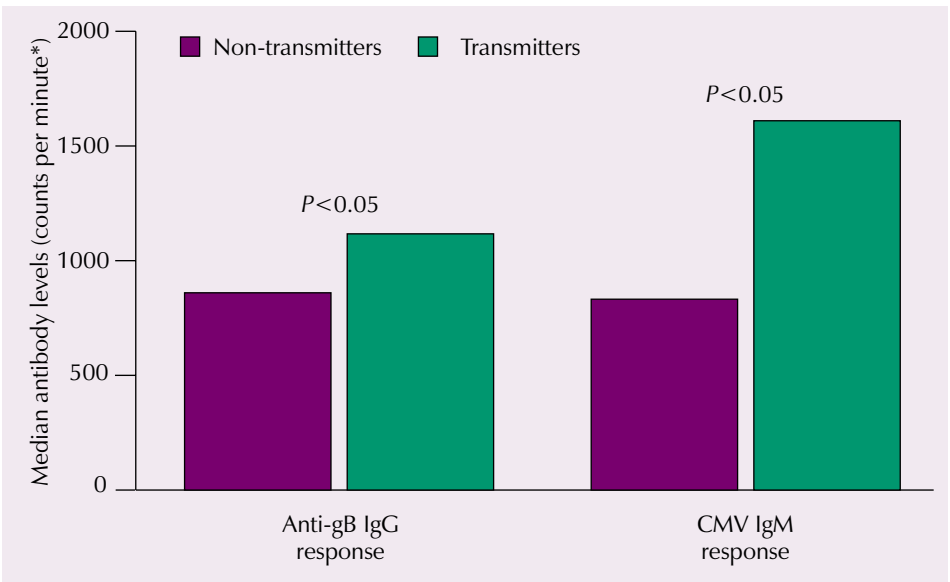

Figure 1: CMV-specific antibody responses in pregnant women who transmitted or did not transmit CMV in utero.[162] **Measured in semiquantitative radioimmunoassay*

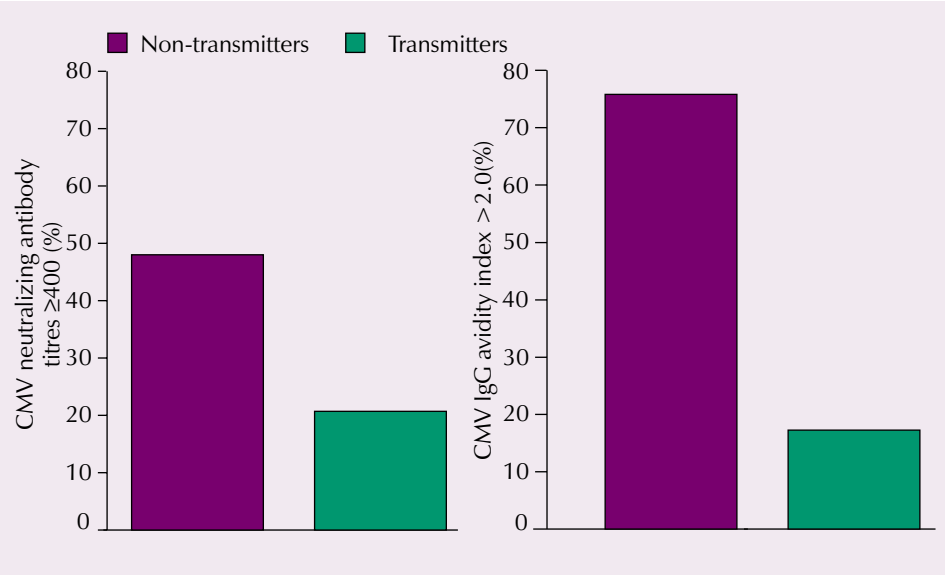

Figure 2: CMV-specific neutralizing antibody titres in pregnant women who transmitted or did not transmit CMV in utero[162]

Further characterization of antibody response revealed a marked difference in the antibody avidity between the two groups of women.[162] The avidity of an antibody is indicative of its functional affinity for an antigen. During the first weeks following infection, antibodies show a low avidity for antigen but as the immune response matures, the antibodies show progressively higher avidity.[166]

High avidity antibody was detected in the serum of more non-transmitters than transmitters.[166] The importance of the avidity of anti-CMV antibodies in outcome has been shown in other studies[167] and for other infections. For example, infants with congenital rubella had significantly lower anti-rubella avidity antibodies than did children who were infected *ex utero*.[168] Because both neutralizing antibody levels and avidity develop relatively slowly (compared with the appearance of antibody) after primary infection, these data suggest that mothers who transmit CMV are in the early stages of primary infection during pregnancy. The failure to produce high-affinity, neutralizing antibodies may result in a greater likelihood of virus dissemination and infection of distant organs including the placenta. This in turn may increase the probability of fetal transmission.

Maternal age

The risk of congenital CMV infection is highest in adolescent women.[169] In an 11-year study in Birmingham, Alabama in the USA, 17 163 newborns of mainly low income, non-white women who delivered at a public hospital, and 9892 offspring of predominately mid to upper income white women who delivered at a private hospital were screened for congenital CMV infection. The study found that in both populations the highest prevalence of clinically apparent infection in newborns was in adolescent women (Figure 3). In both hospitals, the highest prevalence of symptomatic infection was observed in the newborns of mothers younger than 20 years of age.[169] Further, the offspring of the non-white, low income adolescents were at greatest risk for congenital CMV infection and more damaging sequelae.[169] However, a study in the UK found that social class was not associated with the risk of congenital CMV infection.[170]

The occurrence of symptomatic congenital infection usually indicates a primary maternal infection.[160] Thus, the high prevalence of CMV infection in the younger women, especially the non-white, low income teenagers, suggests that a high proportion of congenital CMV infection is due to recent maternal infection and not reactivation of infection. This may be due to more recent, and possibly more frequent, exposure to CMV.[169] In several studies,

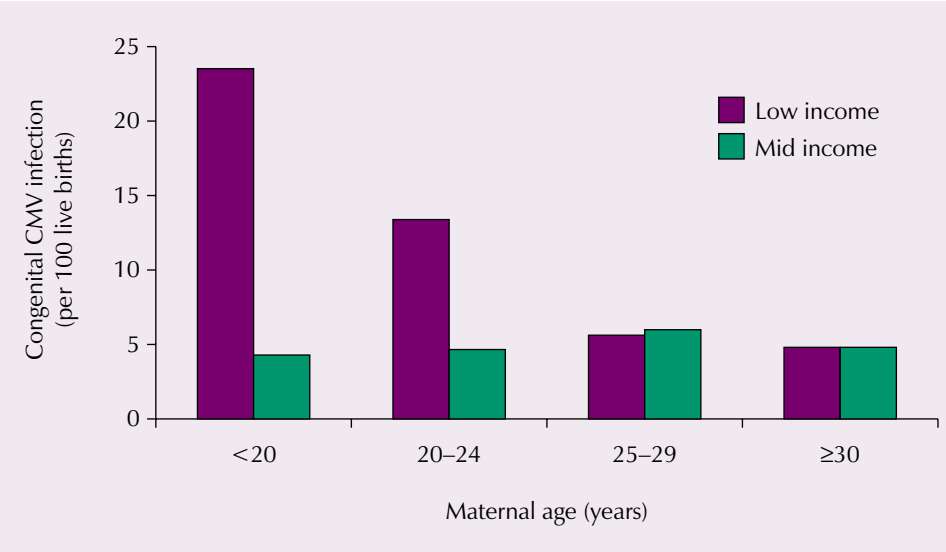

Figure 3: Prevalence of congenital CMV infection by maternal age for newborns screened at two hospitals in Birmingham, Alabama, USA, 1980–1990[169]

seropositivity to CMV has been correlated with the following factors:[144,171]

- Young age at sexual debut
- Number of lifetime partners
- Number of years of sexual activity
- Presence of chlamydial or gonococcal infection.

These studies indicate that sexual activity provides an opportunity for a high level of CMV exposure and may account for the increased risk of congenital CMV infection in non-white, young women.[169] In contrast, the study in Birmingham, Alabama, USA found no association between young maternal age and congenital CMV infection in higher income groups, suggesting that frequent sexual exposure to CMV in adolescence is probably not the principal source of maternal and congenital infection in this population.[169]

Other factors may also contribute to the higher risk of younger women having a newborn with congenital CMV infection. In another study in Birmingham, Alabama, it was found that the prevalence of CMV excretion decreased steadily with age.[172] In 1101 women, the prevalence of CMV excretion peaked at 8% and 15% in the urinary and genital tracts of girls aged 11–14 years and then decreased to undetectable levels in women older than 30 years of age. It is unlikely that the inverse relationship between virus shedding and age is explained by a reduced level of exposure to the virus with increasing age.[32] It has been proposed that the interaction of an age-related factor with recent exposure to the virus in young women may enhance CMV infection during pregnancy and increase the risk of transmission to the fetus.[169]

Impact of CMV Infection on the Pregnant Woman

Most primary and recurrent CMV infections in pregnant women are asymptomatic, although a small proportion may have a variety of clinical symptoms, including an infectious mononucleosis-like illness.

Impact of Congenital CMV Infection on the Neonate

The nature of the maternal infection is a major pathogenetic factor for congenital CMV infection. Primary infection is more likely to be transmitted to the fetus and is more likely to cause fetal injury than recurrent infection.[160]

Sequelae	Per cent symptomatic (no.)	Per cent asymptomatic (no.)
Sensorineural hearing loss	58 (58/100)	7.4 (22/299)
Bilateral hearing loss	37 (37/100)	2.7 (8/299)
Speech threshold: – moderate to profound (60–90 dB)	27 (27/100)	1.7 (5/299)
Chorioretinitis	20.4 (19/93)	2.5 (7/281)
IQ<70	55 (33/60)	3.7 (6/159)
Microcephaly, seizures or paresis/paralysis	51.9 (54/104)	2.7 (9/330)

Table 3: Sequelae in children following congenital CMV infection[173]

As pre-existing maternal antibodies lessen the severity of the sequelae of congenital infection, children of mothers with primary infection are more likely to have symptoms at birth than children of mothers with recurrent infection. The former are also more likely to have functionally important sensorineural hearing loss or be mentally disabled.[160]

The prognosis also differs greatly between infants with congenital CMV infection who are symptomatic at birth and those with no apparent signs of CMV infection at birth (i.e. asymptomatic congenital CMV infection), (Table 3).[173] The risk of CNS sequelae in children born with symptomatic congenital CMV infection is high; approximately 50–90% will experience hearing loss, impaired vision, mental retardation or cerebral palsy, although the severity of handicap varies.[174]

In comparison with children born with sympomatic infection, most children with asymptomatic congenital infection will have normal cognitive and intellectual development within the first 4 years of life.[173,174] However, long-term neurological sequelae will develop in 8–15% of infants with asymptomatic congenital CMV infection.[173,174] The most common outcome is sensorineural hearing loss (see below), although more severe neurodevelopmental deficits, including quadriparesis and microcephaly, have been described.[161] The correlation of asymptomatic congenital CMV infection with learning difficulties is controversial and the impact of this type of infection on development requires further study. Several follow-up studies have demonstrated similar effects of asymptomatic and symptomatic infection neurodevelopment.[161] In contrast, a study in which 18 children with asymptomatic CMV infection were compared with 18 controls matched for age, gender, race, school class (grade) and socioeconomic status found that children with asymptomatic congenital CMV infection and normal hearing were not at increased risk of developing mental impairment.[161]

Sensorineural hearing loss

CMV infection is one of the most important causes of deafness in childhood.[175] The virus can replicate in many structures of the inner ear, the distribution of CMV antigens being more extensive than cytolysis.[176,177] Immune damage may also be a contributing factor to deafness as inflammatory responses are observed in the inner ear.

Sensorineural deafness occurs in up to 58% of newborns with symptomatic congenital CMV infection and up to 15% of children born with asymptomatic infection.[174] The severity of hearing loss is greater in symptomatic children,[174] although it can be progressive in both groups.[178] A cohort of 388 children with congenital CMV infection received audiological evaluations at 3–8 weeks of age, 6 months, 12 months and then annually to assess hearing loss.[178] Sensorineural hearing loss of >20 dB thresholds was detected in 5.2% of all infants at birth, with late onset throughout the first 6 years of life. By the age of 6 years, the cumulative

incidence was 15.4%. The rate of hearing loss was higher in children who were symptomatic at birth than in those without apparent disease (22.8% versus 4.0% at 3 months and 36.4% versus 11.3% at 72 months of age). These findings suggest that universal screening of hearing in neonates will detect less than half of all cases of sensorineural hearing loss caused by congenital CMV infection. Moreover, because most infants with congenital CMV infection are asymptomatic at birth, they will not be recognized as being at risk of sensorineural hearing loss and will not receive further hearing evaluations to detect late-onset hearing loss.

Predictive Features in Congenital CMV Infection

Virus burden in early infancy has promise as a predictor of outcome in congenital CMV infection.[179] CMV viruria and DNA in peripheral blood lymphocytes (PBL) were examined in 82 infants. The presence of CMV DNA in PBL did not correlate with an adverse outcome although virus burden did. In children in whom CMV burden was quantified, children with sequelae had a higher virus load and also higher urine CMV titres than those without sequelae.

Studies examining clinical abnormalities in relation to mental retardation found that chorioretinitis, microcephaly and an abnormal neurological examination or cranial computed tomographic (CT) scan at infancy had predictive value.[180]

Retinitis

The presence of retinitis, which is found in 10–15% of symptomatic neonates, correlates best with neurological damage.[174,180] A long-term study that followed up 32 symptomatic children found that all children with retinitis had significant mental retardation whether or not they were visually impaired.[180]

Microcephaly

Microcephaly at birth is predictive of later neurological sequelae, although the risk is not as great as for retinitis.[180] This clinical finding is present in over 50–70% of infants who are symptomatic at birth,[161,181] although symptomatic newborns with a normal head circumference may become microcephalic.[181]

Other neurological findings

Abnormal neurological examination result at 1 year of age is associated with later mental retardation. Whether or not other abnormal neurological findings such as lethargy, hypotonia, poor suck and seizures can predict sequelae is not known.

Reticuloendothelial involvement

In contrast to CNS involvement, evidence of reticuloendothelial system involvement, as indicated by thrombocytopenia and hepatic abnormalities, as well as prematurity and growth retardation have not been shown to be predictive of neurological outcome (Table 4).

CT scan findings

In neonates with symptomatic congenital CMV infection, a computed tomography (CT) scan is a good predictor of an adverse neurodevelopmental outcome.[182] In a retrospective analysis, data from 56 children with symptomatic congenital CMV infection who underwent CT scans as newborns, and who were enrolled in a long-term follow-up study were analysed. Abnormal CT scans were noted in 70% of subjects, with the most common finding being intracerebral calcification. The majority of children with an abnormal newborn CT scan (90%) developed at least one sequela, compared with 29% of those with a normal finding. Newborn CT abnormalities were associated with low IQ (<70), an abnormal hearing screen at birth and hearing loss on follow-up. None of the neonatal neurological findings were predictive of an abnormal CT scan.[182] The study also examined the relationship between CT scan results and other newborn findings (clinical and laboratory), and found that they did not predict neuroradiographic abnormalities.[182] Thus, the appearance of clinical findings of CNS involvement at birth can help the physician counsel parents and plan long-term follow-up for these children.

Only site of maternal infection	No. of infants infected/no. exposed	(%)
Breast milk		
Breast-fed infant	19/30	63
Bottle-fed infant	0/9	0
Cervix		
Third trimester and post-partum	8/14	57
Third trimester	18/68	26
Second and third trimester	1/8	12
Urine	0/11	0
Saliva	0/15	0
Non-excreting women		
Breast-fed infant	0/125	0
Bottle-fed infant	0/11	0

Table 4: Association between maternal excretion of CMV from various sites and infection of infant[183]

Perinatal CMV Infection

Perinatal or post-natal CMV transmission in infants occurs during exposure to infected genital secretions at birth, through breast milk, or through blood transfusion from a seropositive donor.[183] The two most common sources of transmission in the perinatal period are the genital tract and breast milk (Table 4).[183] Infected breast milk has been demonstrated to account for 63% of perinatal acquisitions whereas the infected genital tract, particularly in late gestation, was associated with transmission in 26–57% of cases.[183] The incubation period of perinatal CMV infection ranges from 4 to 12 weeks. The infection is chronic, with shedding persisting for years.[133]

Whether resulting from transmission during delivery, via breast milk or, less commonly, through blood transfusion, perinatal CMV infection is associated with much less morbidity compared with congenital CMV infection. Perinatal infection often involves the hepatobiliary tract but rarely causes clinical manifestations in normal individuals and is occasionally associated with protracted interstitial pneumonitis.[158]

Conclusions

The factors that influence the transmission of CMV to the neonate and mediate damage to the fetus have not been defined fully. A pre-existing CMV-specific humoral response can lessen the deleterious effects on the fetus, but in contrast to congenital rubella or toxoplasmosis, maternal antibody does not completely protect the fetus. Thus, although congenital CMV infection is more likely in a seronegative pregnant woman who has primary CMV infection during pregnancy, CMV-infected infants can be born to women with recurrent infection.

Symptomatic infection occurs in 5–10% of congenitally infected infants, with over 90% of these children experiencing motor, visual, cognitive or auditory sequelae. The remaining 90% of congenitally infected infants will have no obvious signs or symptoms of CMV infection but many of these (approximately 11%) will subsequently develop sensorineural hearing loss. Overall, intra-uterine CMV infection is one of the major causes of sensorineural hearing loss worldwide.

The neurodevelopmental sequelae associated with congenital CMV infection and the developmental consequences of CMV-induced sensorineural hearing loss are such that identification of the pregnant woman or neonate may have value, but any diagnostic or screening measure should be balanced against the availability, and efficacy, of an intervention.

Summary

CMV is the leading cause of congenital virus infection in the world. Approximately 1% of all infants are congenitally infected; the prevalence of infection ranges from 0.2% to greater than 3%.

Sociodemographic factors such as urban residence, ethnic origin and socioeconomic status affect the rate of CMV acquisition. In women of child-bearing age, intrafamilial and sexual transmission of CMV are important.

Transmission of CMV from mother to fetus may occur during all three trimesters. The consequences of infection on the fetus are generally worse when it occurs in the first half of pregnancy.

CMV is unusual among viruses causing congenital infections in that it can be transmitted *in utero* and cause disease during primary or recurrent infections. The transmission rate is higher during primary infection than in recurrent infection indicating that maternal immunity provides some protection against congenital CMV infection.

The presence of maternal immunity to CMV before conception lessens the risk of *in utero* transmission. The IgG and IgM antibody titres are higher in women who transmit CMV *in utero* compared with those who do not. Moreover, the titres of neutralizing antibody and avidity index are higher in women who do not transmit virus.

The prognosis differs greatly between infants with congenital CMV infection who are symptomatic and those who are asymptomatic at birth. The risk of CNS sequelae in children born with symptomatic congenital CMV infection is high. Most children with asymptomatic congenital infection will have normal cognitive and intellectual development, but 8–15% of these infants will have complications of which the most common outcome is sensorineural hearing loss.

Studies examining clinical abnormalities in relation to mental retardation found that virus burden, chorioretinitis, microcephaly and an abnormal neurological examination or CT scan at infancy have predictive value for adverse neuroimpairment. Virus load may also be predictive of outcome.

Perinatal CMV infection is largely asymptomatic with no apparent adverse effects on growth, motor or psychosocial development.

Management of Cytomegalovirus Infection in the Pregnant Woman and Neonate

Diagnosis of Cytomegalovirus Infection in the Pregnant Woman

Over 90% of cytomegalovirus (CMV) primary infections in pregnant women, as in most otherwise healthy individuals, are asymptomatic and likely to remain undetected by the woman and her physician. In addition, symptomatic infection is usually accompanied by symptoms that are non-specific for CMV, including fever, fatigue, headache, myalgia and sore throat. Given the impact of CMV infection on the fetus, definitive identification of the serostatus of the pregnant woman and whether or not the infection is active are necessary. A differential approach based on pre-conception serostatus is provided below (Figure 1).

Determination of Pre-Conception Serostatus

Woman whose CMV serostatus before conception is known

For women who are known to be seropositive for CMV before conception, the rate of fetal infection is less than 1%[134] and, even where transmission occurs, it is linked to less severe sequelae of congenital CMV infection than infection in seronegative women.[160] Thus, for women who are known to be seropositive before conception, there is no requirement for laboratory CMV testing unless indicated by particular clinical characteristics of the mother or fetus (Figure 1).

In comparison, women seronegative for CMV before conception are susceptible to primary CMV infection. Good hygiene practice and advice on sex (e.g. use of condoms, abstinence, frequent handwashing, avoiding direct contact with secretions) should be given to these women. This is of particular importance for those who routinely come into contact with

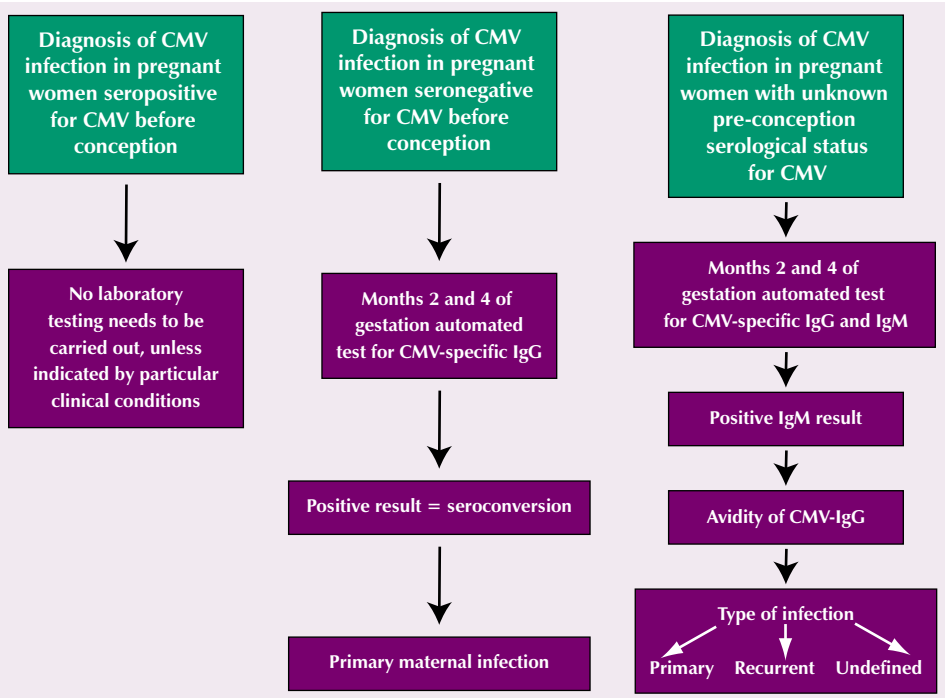

Figure 1: Proposed scheme for diagnosis of pregnant women according to their CMV serological status

young children as they can excrete virus for months in the absence of clinical signs. However, such mechanical measures may be impracticable, especially for mothers of young children.

In seronegative women, serological testing for CMV-specific immunoglobulin (Ig) G may be performed at two different time points during pregnancy (i.e. months 2 and 4). If the women is seronegative at both tests, follow-up may be suspended. Where seroconversion is detected, pre-natal diagnosis should be offered to determine the likelihood of intra-uterine infection and the risks associated with the diagnostic procedure explained (Figure 1).

Serological testing for IgG can be performed using available commercial tests. These have reasonable sensitivity and specificity, although there is cross-reactivity with other members of the Herpesviridae family[184] which can give rise to false positives. Assays are being developed that use selected recombinant antigens instead of virus particles or lysates, which should reduce the problem of cross-reactivity.

Woman whose pre-pregnancy serological status is unknown

The diagnosis of CMV infection is complex in the woman whose pre-pregnancy serological status is unknown. As most CMV infection is asymptomatic, it is difficult to identify pregnant women undergoing acute, asymptomatic infection. A solution is to screen all pregnant women, although many countries do not screen for CMV disease during pregnancy because of:

- Cost
- Unreliability of tests
- It is not possible to identify fetuses at risk where women with a primary infection are identified
- Lack of treatment options.

The most appropriate procedure for screening pregnant women is CMV-specific IgM detection. However, the correlation between results obtained from commercial assays that detect IgM is poor, which limits their value.[185,186] Serological diagnosis may be improved with the advent of a new generation of serological tests containing a mixture of genetically defined CMV antigens.[187–189] The high sensitivity and the relatively low cost of these tests makes them suitable screening tests for pregnant women whose pre-conception CMV serostatus is unknown.

Routine serological screening of pregnant women for CMV infection cannot be recommended as a standard of care at the present time. If antiviral therapy which can safely prevent or treat fetal infection is developed then the role of maternal pre-natal screening must be reassessed. Screening some high-risk women or populations may be of value now, although choices for intervention are limited.

It may be appropriate to store the first antenatal screening blood sample for a minimum of 12 months and to analyse it where indicated clinically (e.g. fever of unknown origin; cervical lymphadenopathy).

Identification of Primary CMV Infection

Diagnosis of primary CMV infection in the mother can be performed by serological and virological methods.

Serological tests: CMV-specific IgM

CMV-specific IgM is a sensitive indicator of ongoing or recent infection but, although it indicates a primary infection, less than 10% of IgM positive women will have a congenitally infected fetus or newborn.[190] This is partly because IgM is often produced during reactivation or re-infection, and the IgM titre at the beginning of an infection may be similar to that during a recurrence[191–193] with the result that false positives are common. Thus, the presence of IgM, or a high titre of IgM, should not be the sole method for identifying primary CMV infection; a positive IgM test should be considered only as the starting point for a more thorough diagnostic evaluation.

Serological tests: IgG avidity and IgM reactivity by immunoblot

Primary infection can be reliably determined by measuring IgG avidity. A low IgG avidity is a marker of primary CMV infection in immunocompetent subjects for 18–20 weeks after the onset of symptoms.[186,194] In both pregnant and solid organ transplant recipients, anti-CMV IgG avidity, determined using a commercially available enzyme immunoassay, reliably distinguishes between primary and non-primary CMV infection.[167] In more than 90% of primary infections, IgG to CMV was of low avidity whereas low avidity IgG was not detected in non-primary infections.[167]

In serum obtained during the first trimester of pregnancy, a CMV IgG avidity index above 65% is not associated with congenital CMV infection.[195] In a study of 78 women without a documented seroconversion history, and with a CMV-specific IgM response or equivocal result on first testing during pregnancy, eight cases of congenital CMV infection occurred in women whose avidity index was less than 50%. Congenital infection in the first trimester was not associated with an intermediate or high CMV IgG avidity index.[195] The results of the above investigation are corroborated by a study in 41 women with CMV-specific IgM and without seroconversion. Of 41 infants, four had congenital CMV infection and each of these was born to a mother with a CMV IgG avidity index below 30%.[194]

The reactivity of IgM to different CMV proteins, as detected by immunoblotting, has also been shown to be useful for identifying pregnant women at risk of transmitting the virus to their fetus.[186] The utility of these two measures in determining the risk of transmission was examined in a study of 87 pregnant women.[196] The results indicated that if the anti-CMV IgM antibody avidity is measured before 18 weeks' gestation, it can identify all pregnant women who will give birth to an infected newborn. In contrast, IgM detected by immunoblotting showed a sensitivity of only 69%. Later in gestation (20–23 weeks), the sensitivity of IgM detection by immunoblot is greater than that obtained by avidity (75% and 63%, respectively). Thus, the early determination of anti-CMV antibody avidity is a helpful tool to identify a subgroup of women at risk of transmitting infection whereas if assessment is performed later in pregnancy, an IgM immunoblot may be of value. A major drawback for the use of immunoblot is that the test is not commercially available.

Although laboratory assays can identify primary CMV infections, no assays exist to detect recurrent infection that may be transmitted to the fetus.

Antigen detection

The use of maternal CMV viraemia or CMV antigenaemia for diagnosis has received little attention because of the difficulty of isolating the virus or antigens in blood, and as CMV can be detected in the blood of pregnant women during recent primary or ongoing infections.[197,198] Initial findings in one study indicate that the risk of congenital CMV infection is increased 10-fold in viraemic mothers compared with those without evidence of viraemia.[197] In contrast, another study found that virus levels determined by antigenaemia, viraemia and DNAaemia were low and did not correlate with clinical course of infection, intra-uterine transmission or severity of outcome.[198] In this latter study, the sensitivities of the antigenaemia and viraemia tests were low, detecting only 50% and 25% of patients in the first month after infection, whereas at 2 months only 25% of patients were antigenaemia-positive and none were positive for viraemia. CMV DNA was detected in peripheral blood leucocytes in 100% and 90% of subjects examined after 1 and 2 months, respectively, and persisted for 6 months. The persistence of CMV DNA for 3 months or longer was not associated with a higher risk of fetal infection.

Pre-Natal Diagnosis (Amniocentesis)

Definitive pre-natal diagnosis is required, as the only available intervention for congenital CMV infection is termination of pregnancy. Pre-natal diagnosis could be offered to pregnant women who develop a primary infection or an undetermined type of CMV infection characterized by a high virus load (as shown by viraemia) during the first half of gestation. In approximately 70% of cases, the results will indicate an absence of fetal infection, preventing unnecessary termination of uninfected fetuses and allowing women to continue their

pregnancies with a high level of confidence. If an *in utero* treatment becomes available, pre-natal diagnosis of CMV infection and treatment before the fetus is irreversibly damaged might have a significant effect on the course of disease.[199,200]

How to perform pre-natal diagnosis

Material to test

Amniotic fluid is a suitable choice of body fluid for the pre-natal diagnosis of CMV infection as, although the precise mechanisms of fetal infection are not fully understood, the fetus excretes CMV via urine into the amniotic fluid.[201–207]

Optimum time to perform amniocentesis

The optimum time to perform amniocentesis is between 21 and 23 weeks' gestation as:

- False negative results have been reported before this age, as fetal diuresis becomes established only after 20–21 weeks' gestation
- In most cases, 6–9 weeks must elapse from the time of maternal infection before virus can be detected in amniotic fluid, and CMV infection is correlated with severe fetal disease principally when it occurs during the first 12 weeks' gestation.[208]

It is possible that CMV infection occurring at the beginning of the pregnancy may not be detected with amniocentesis, but this is unlikely as fetal excretion of the virus may last for months, as in congenitally infected newborns. Amniotic fluid taken at 21–23 weeks' gestation should still test positive even when the infection has occurred during the first weeks of pregnancy. Importantly, as terminations are not legally allowed after 20 weeks in some countries, pre-natal diagnosis may have to be performed earlier. The lower sensitivity of the test in this situation should be taken into account.

Choice of assay

A large-scale study compared polymerase chain reaction (PCR) with virus isolation for pre-natal diagnosis of congenital CMV infection using amniotic fluid from 82 pregnancies at risk of transmitting CMV (Table 1).[193] In 50 cases, fetal blood was also obtained and both antigenaemia and PCR performed. The results indicated that amniotic fluid is better for pre-natal diagnosis than fetal blood (Table 1).

Material	Test	Sensitivity (%)	Specificity (%)	PPV	NPV
Amniotic fluid	PCR	100	83.3	0.48	1.00
	Shell vial assay	50	100	1.00	0.94
Fetal blood	PCR	66.6	85.5	0.33	0.96
p65 antigenaemia	Rapid virus isolation	16	98.2	0.50	0.92

PPV: positive predictive value; NPV: negative predictive value

Table 1: Performance of antigenaemia and PCR in the detection of congenital CMV infection[193]

The positive predictive value of 0.48 for PCR in the study indicates that detection of CMV DNA in amniotic fluid is of limited diagnostic value. A positive isolation is indicative of congenital infection but false negatives are not uncommon because intact virus particles are required to be infectious for detection in culture. To avoid the risk of false negative results, 3–6 replicates of amniotic fluid samples (depending on the available amount of the sample) should be amplified independently in routine diagnosis.[206]

How to Identify Fetuses at Risk of CMV Disease

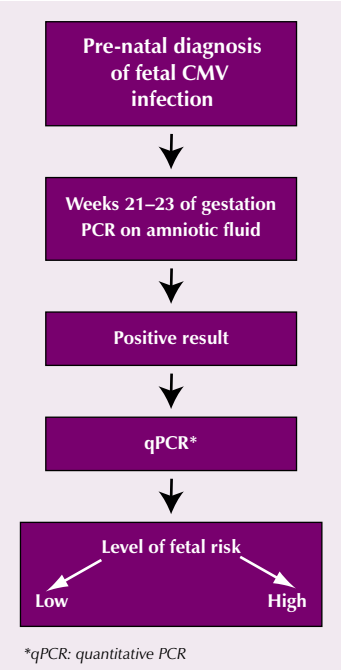

Figure 2: Proposed scheme for pre-natal diagnosis of fetal CMV infection.

In approximately 30% of cases, intra-uterine transmission will be documented, but does not necessarily mean that the fetus will have disease. Therefore, a further diagnostic problem of identifying fetuses at risk of severe CMV disease arises.

Until recently, fetuses at high risk of infection have been identified by fetal ultrasound as part of a woman's routine pre-natal care. As other intra-uterine infections (herpes simplex virus, varicella zoster virus, HIV, rubella, syphilis and toxoplasmosis) can cause similar clinical findings, a differential diagnosis should be made.[209,210] In many cases, clinical signs may be identified too late to allow pregnancy termination. In those cases with documented CMV transmission, determination of virus load in the amniotic fluid by quantitative PCR seems to be able to identify fetuses at higher risk of developing a severe infection.[196] A management scheme for pre-natal diagnosis of fetal CMV infection is proposed in Figure 2.

Post-Natal Diagnosis

The standard diagnostic test for congenital CMV infection is detection of virus in urine and/or saliva collected as soon as possible, certainly within the first 3 weeks of life. An alternative is CMV-specific IgM determination in serum, although CMV-specific IgM can only be detected in about 70% of newborns.[211]

PCR of the serum for CMV DNA has proven to be a rapid, sensitive and specific method for the diagnosis of congenital CMV infection in infants who are asymptomatic at birth. In a comparison of urine CMV culture (gold standard) with IgM determination and serum PCR in infants with congenital CMV infection, serum PCR was the most sensitive and specific test (Table 2).[212] PCR of the urine also has high sensitivity compared with tissue culture,[213,214] and PCR of the cerebrospinal fluid (CSF) may also be of value in the rapid diagnosis of CMV infection in neonates.[215]

	No. of patients (%)			
Laboratory evaluation	**With symptomatic congenital CMV infection *n*=18 (%)**	**With asymptomatic congenital CMV infection *n*=2 (%)**	**Uninfected *n*=32 (%)**	**Sensitivity (%) and specificity (%) compared with urine CMV culture in symptomatic congenital CMV infection**
Urine CMV culture positive	18 (100)	2 (100)	0 (0)	–
CMV IgM positive	4 (22)	0 (0)	0 (0)	Sens: 22 Spec: 100
Serum PCR positive by liquid hybridization	18 (100)	1 (50)	0 (0)	Sens: 100 Spec: 100

Table 2: Results of urine CMV culture, serum PCR and serum IgM antibody in congenitally infected and uninfected neonates[212]

After 21 days – because serology and virus detection will not distinguish pre- and post-natal infection – diagnosis should rely on clinical suspicion based on the typical pattern of signs and symptoms.[216] Clinical findings and neuroimaging allow diagnosis of CMV infection in the neonate. Some of the more common clinical manifestations are shown in Table 3.[217]

Physical finding	Laboratory finding
Intra-uterine growth restriction	Thrombocytopaenia
Non-immune hydrops	Elevated serum transaminase enzymes
Microcephaly	
Ventriculomegaly	
Periventricular calcification	
Intrahepatic calcification	
Hepatosplenomegaly	
Chorioretinitis	
Pseudomeconium ileus	
Sensorineural hearing loss	

Table 3: Physical and laboratory findings in congenital CMV infection[217]

As over 90% of newborns with congenital CMV infection are asymptomatic at birth, they will not be diagnosed unless newborns are screened. Screening for congenital CMV infection can be accomplished accurately by testing saliva or urine for virus but universal screening cannot be recommended until data supporting cost-effectiveness are available. Although isolation of CMV from urine or saliva is the gold standard for diagnosis or screening, PCR detection should work well for diagnosis, but it has not been adequately evaluated for screening purposes.

Finding	Per cent affected†
No abnormalities	30
Intracerebral calcifications	70
Calcifications + other abnormality	56
Ventricular dilation	10
Cortical and/or migration abnormality	8

†*Neonates with symptomatic congenital CMV infection*

Table 4: Cranial CT scans in 56 newborns with symptomatic congenital CMV infection[182]

Neuroimaging may reveal intracranial calcifications, dilated ventricles, enlarged subarachnoid space, oligo/pachygyria, abnormal myelination and paraventricular cysts (Table 4).[182,218] These sequelae are clinically more prominent following infection early in pregnancy than later.[216] A cranial computed tomographic (CT) scan is a good predictor of adverse neurodevelopmental outcome in neonates with symptomatic congenital CMV infection.[182]

PCR performed on dried blood stored on filter paper has been shown to allow retrospective diagnosis of congenital CMV infection.[219] Consideration, however, should be given to the possibility of contamination from adjacent blood samples. Demonstration projects are required to determine if Guthrie cards can distinguish between intra-uterine and post-natally acquired CMV infection.

Follow-Up

There are no available means to prevent hearing loss in infants and children infected with CMV *in utero*. Despite this, the ability to detect CMV in the pre-natal or post-natal period has several benefits as it can:[148]

- Provide explanations for hearing loss in otherwise healthy infants
- Justify serial audiometry given the possibility of progressive hearing loss
- Facilitate implementation of intervention programmes designed to maximize speech and language development
- Allow cochlear implants to be used to treat sensorineural hearing loss in children.[220,221]

Universal screening of hearing in neonates will detect less than half of all cases of sensorineural hearing loss caused by congenital CMV infection and most infants are asymptomatic at birth but are at risk of progressive hearing loss. Therefore, infants and children with congenital CMV infection should have audiological evaluations at least twice a year for the first 3 years of life and annually up to school age because of the risk of progressive and late onset hearing loss. Every infant with congenital CMV infection should have at least one fundoscopic examination for retinal lesions. If lesions are present, the follow-up examinations are recommended at least annually. If any impairments are found,

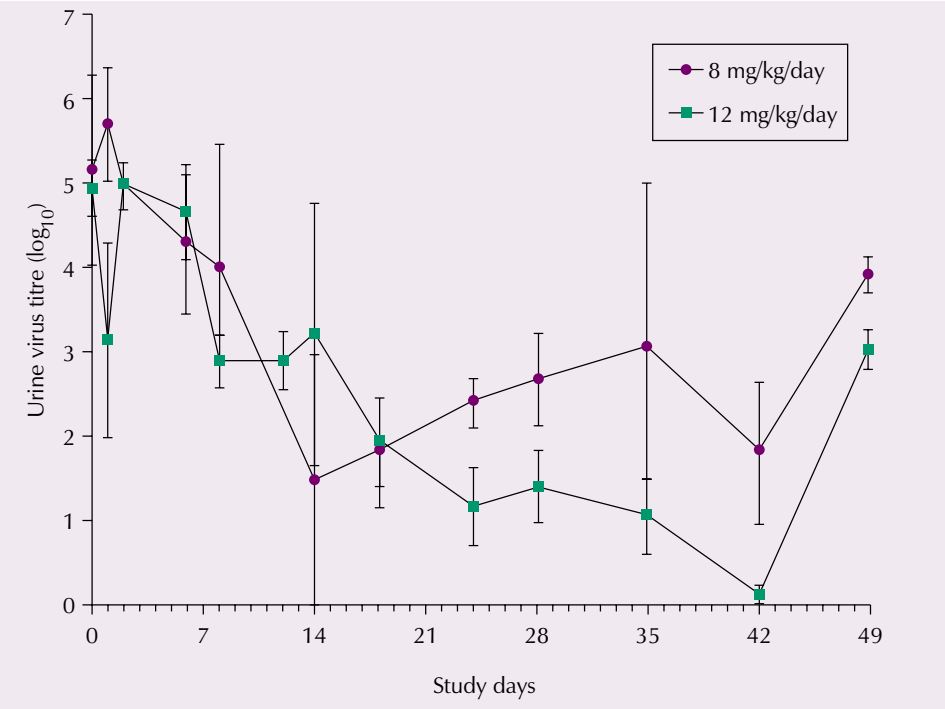

Figure 3: Comparison of CMV titres in urine of children who received ganciclovir 8 versus 12 mg/kg/day[200]

infants and children with congenital CMV infection should receive services aimed at maximizing their hearing, speech, vision, cognitive and motor functions.

Treatment

Ganciclovir

Ganciclovir, foscarnet and cidofovir are used for the treatment of life- or sight-threatening CMV disease in immunosuppressed patients, particularly those with AIDS. Of these agents, only ganciclovir has been evaluated in the treatment of infants with symptomatic congenital CMV disease.[200, 222]

An uncontrolled Phase II pharmacokinetic, pharmacodynamic and safety evaluation of ganciclovir included preliminary estimates of neurological efficacy (e.g. hearing loss). The agent was selected for use because of its significant antiviral activity but, owing to the drug's known toxicity, only children at exceedingly high risk of death or severe neurological impairment were selected for entry into the protocol.[200]

Ganciclovir 8 or 12 mg/kg daily was administered in divided doses at 12-hour intervals for 6 weeks. A total of 14 and 28 infants received 8 and 12 mg/kg day, respectively, with five infants receiving ganciclovir on a compassionate basis.

The most common adverse event observed was absolute neutropaenia (≤500 mm^3), which was evident in 10 children (63%) who received 8 mg/kg/day and in six (19%) who received 12 mg/kg/day. This adverse event required dosage adjustment. Other adverse events, which were encountered in a significant number of children and required dosage modification, were thrombocytopaenia and elevated results of liver function tests. Overall, 81% of the children completed the 6-week treatment course with ganciclovir.

Ganciclovir 12 mg/kg/day produced a more pronounced antiviral effect, as measured by CMV titres in the urine, compared with the lower dose (Figure 3). All children who excreted virus in the urine had a subsequent return of virus in urine following discontinuation of therapy, although the levels were slightly lower than those at the initiation of treatment. Throat wash cultures and white blood cell (WBC) cultures were also assessed in a subset of infants. A significant reduction in the quantity of virus at these sites was found (Table 5).

	Throat wash culture No. positive/total tested	WBC culture No. positive/total tested
Positive at study entry	14/20	3/7
Positive after 2 weeks' therapy	3/5	0/3
Positive after 6 weeks' therapy	0/4	nd

nd = not done

Table 5: Virological evaluations of ganciclovir therapy

The efficacy of ganciclovir was indicated by its effects on the infants' hearing. Hearing improvement or stabilization occurred in five of 30 infants (16%) at 6 months or later (Table 6). It was also noted that the CMV-related mortality rate of 6% was possibly lower than in retrospective studies in patient populations significantly less ill than those in this trial of ganciclovir. In addition, the percentage of study children who appeared to be developing normally 2 years after the onset of therapy (24%) was judged to be in excess of that anticipated from the literature. In considering the results, the authors emphasized that, owing to the small sample size of this Phase II trial, the data do not provide adequate evidence of efficacy to warrant routine use.[200]

Audiology evaluation at 6 months (Brainstem-evoked potential)	Number (%) (*n*=30)
Normal → Normal	2 (6)
Abnormal → Normal	3 (10)
Normal → Abnormal	11 (37)
Abnormal → Abnormal	14 (47)

Table 6: Clinical outcome in children receiving ganciclovir 8 or 12 mg/kg/day

A second study has evaluated ganciclovir in 12 children with CMV infection. Six infants were given ganciclovir, 5 mg/kg twice daily for 2 weeks (Group 1); the other six infants received 7.5 mg/kg twice daily for 2 weeks and 10 mg/kg three times weekly for 3 months (Group 2).[222] Adverse effects of ganciclovir were observed only in infants in Group 2; all effects were mild and transient and none required discontinuation. Virological and laboratory data also indicated that efficacy of ganciclovir was related to higher dosage or longer duration of therapy or both. Normal clinical outcome was observed in only two patients in Group 1. In comparison, clinical improvement was evident in five infants in Group 2, although one had later development of mild psychomotor retardation and in another infant, severe psychomotor retardation and hearing loss developed after transient improvement. In common with the trial described above, the small sample size limits the conclusions about the efficacy of ganciclovir. Importantly, the expected course of untreated symptomatic congenital CMV infection is spontaneous improvement of newborn hepatic and haematological abnormalities during the first few weeks of life.[174]

In summary, currently, no antiviral treatment for congenital CMV infection has been shown to decrease the frequency or severity of CNS damage in controlled clinical trials. It is possible that the use of ganciclovir in some newborns with cytomegalic inclusion disease could decrease mortality or severe morbidity in the newborn period. Compassionate use of ganciclovir in newborns with life-threatening or vision-threatening congenital CMV infection is probably justified. It should be noted that there is currently no method of proven efficacy for preventing maternal infection during pregnancy.

Future treatment options

There are two time periods for the treatment of congenital CMV infection: *in utero* and post-delivery. Each of these options has its own challenges for the development of treatments.

In utero treatment

In utero treatment is limited currently by the inability to identify infected women at risk of intra-uterine transmission of CMV. More accurate approaches are in development for

identifying the risk of transmission during primary infection, but there is no pre-natal marker for immune mothers who will transmit CMV or for the fetus with disease. Ganciclovir is limited by its potential for toxicity and mutagenicity. Any antiviral developed must have a low risk for fetal toxicity, especially given that in recurrent maternal infection the risk of CMV damage to the fetus is 0.8/1000 births.

Benzimadazole ribonucleosides

Possible candidates for the treatment of maternal and congenital CMV infection are the benzimadazole ribonucleosides. They inhibit CMV replication late in the cycle without inhibiting viral DNA synthesis. This is achieved by inhibiting formation of the monomeric genome from the polygenic concatemer.[223] This inhibition of DNA maturation is probably mediated through interaction with a terminase, which is thought to be the UL89 gene product. As mammalian DNA maturation does not involve a DNA maturation step, compounds such as the benzimadazole ribonucloesides should be selective and safe.[223] The benzimadazole, benzimdizir, has also been shown to be an inhibitor of UL97, a phosphotransferase. As a class, the benzimadazoles show a potent anti-CMV effect, a favourable pre-clinical toxicity profile and good oral bioavailability.[223,224]

Passive immunotherapy

Passive immunotherapy is a potential alternative to antiviral treatment. In the first report of fetal immunotherapy, CMV hyperimmunoglobulin was injected into the fetal abdominal cavity at 28 and 29 weeks of pregnancy.[199] Urine cultures at birth were positive and a brain CT scan performed at 2 weeks revealed signs of congenital CMV infection. In a second case report, high-titre CMV neutralizing antibodies were administered to a woman with primary infection and placental involvement of a twin fetus. After infusion of the CMV immunoglobulin, placental oedema reduced and the infected fetus started to grow again. CMV DNA was detected in the other twin 1 week after birth.[225] It is difficult to draw any conclusions about the efficacy of CMV hyperimmunoglobulin from these two case studies.

Prevention of Congenital CMV Infection

There is currently no method of proven efficacy for preventing maternal CMV infection during pregnancy.

Vaccination

A vaccine for CMV may be able to prevent primary infection, but is unlikely to reduce *in utero* transmission as a result of reactivation. Despite this, preventing primary infection alone may be worthwhile because of the greater risk associated with this type of infection.

As yet, there is no licensed vaccine for active immunization and none has been specifically tested in pregnant women. A number of candidate vaccines are in development (Table 7). A live attenuated strain of CMV (Towne) has been shown to achieve immunity similar to that provided by wild type infection in three open-label trials involving 68 men, 63 women of childbearing age and 13 children, respectively.[226] Lymphoproliferative responses to CMV were measured in 45 subjects and all had positive responses. Neutralizing antibody titres were maximal at 2 to 4 months' post-immunization, were dose-dependent and were similar to those induced by natural infection. Although these studies were not conducted in pregnant women, their results support further evaluation of the Towne strain of CMV in women at risk of acquiring CMV infection during pregnancy.

A recombinant subunit (gB) vaccine administered with MF59 adjuvant is currently being developed. It is well tolerated and immunogenic although the antibody response wanes with time.[227] A Phase II trial is being considered in women who are seronegative at the birth of their first child and who are followed to their next pregnancy. The primary outcomes will be maternal infection and rate of congenital CMV infection in a subsequent pregnancy.

Vaccine	Composition	Manufacturer
Towne	Live virus	Merck/Microbiological Associates
CMVgB	Recombinant gB/MF59	Chiron Vaccines
ALVAC-CMVgB	Viral vector/recombinant gB	Pasteur-Merieux Connaught
Chimeric CMV	Live virus, recombinant	Towne/Toledo, Aviron

Table 7: Investigational CMV vaccines

Other candidate vaccines include a Canarypox vaccine (ALVAC) incorporating recombinant gB. This has completed early Phase I trials and is now in a Phase I trial in which it is administered together with the recombinant gB vaccine. A live chimera of Towne and Toledo CMV strains is in clinical development.

Behavioural intervention

A study evaluating behavioural approaches to reduce child-to-parent transmission suggests that advice on protective behaviours (e.g. frequent handwashing, avoiding intimate contact) is not particularly effective.[139] In CMV seronegative mothers who received education about protective behaviours either with or without social reinforcement, up to 36% seroconverted over 8 months compared with 47% in the control group.[139] Thus, it is unlikely that measures involving hygiene precautions alone will reduce the risk of a seronegative woman acquiring CMV. This is especially true if the woman already has children or is employed in child care. However, preventative hygienic strategies should continue to be investigated.

Summary and Management Recommendations

Natural history of CMV infection in pregnancy

Most maternal CMV infection is asymptomatic. Those infections that are symptomatic are usually accompanied by non-specific symptoms. As maternal CMV infection, particularly primary infection, can have adverse consequences for the fetus, definitive identification of the seronegative pregnant woman is required.

Primary maternal CMV infection represents more of a risk to the fetus than recurrent maternal infection. Primary and recurrent CMV infections in the mother are usually asymptomatic (*Category 1 recommendation*).

Laboratory assays can reliably identify primary infection but are not yet widely available. No assays exist to detect recurrent infection in the mother that may be transmitted to the fetus (*Research need recommendation*).

Pre-natal screening and diagnosis

For women known to be seropositive before conception, no further laboratory tests for CMV need be performed. For the woman who is known to be seronegative before conception, testing for CMV-specific IgG can be considered at two different time points during pregnancy if she is at risk (i.e. day care workers, those who work with children or who have multiple partners). If seronegativity persists, follow-up can be suspended but if seroconversion takes place, then pre-natal diagnosis should be offered.

Consideration should be given to testing women whose pre-conception serostatus is unknown for CMV-specific IgM using a reliable assay. The presence of IgM is an indicator of ongoing or recent infection, but by itself is not a specific indicator of primary infection.

The most reliable indicator of CMV infection is low avidity CMV specific IgG which should be performed before 18 weeks' gestation and should be considered by reference laboratories.

Routine serological screening of pregnant women for CMV infection cannot be recommended as a standard of care at the present time. If antiviral therapy that can safely prevent or treat fetal infection is developed then the role of maternal pre-natal screening must be reassessed. Screening some high-risk women or populations may be of value now, although choices for intervention are limited (*Research need recommendation*).

The optimum time to perform amniocentesis is between 21 and 23 weeks' gestation as CMV infection is correlated with severe fetal disease when it occurs in the first 12 weeks of pregnancy, at least 6 weeks must pass from the time of maternal infection before virus can be detected in the amniotic fluid. Further, fetal diuresis only becomes established after 20–21 weeks' gestation. The virus in amniotic fluid can be detected by PCR or culture but neither can predict fetal outcome. Preliminary results suggest that virus load, as determined by quantitative PCR, can identify fetuses at higher risk of developing a severe infection. In countries where termination after 20 weeks is illegal, consideration should be given to performing the test before 20 weeks.

Fetal CMV infection can be diagnosed accurately by detection of virus in amniotic fluid by culture or PCR. However, routine screening for fetal CMV infection during pregnancy is not indicated at present. This should be reviewed if a therapeutic intervention of proven value becomes available (*Research need recommendation*).

Screening for and diagnosis of congenital CMV infection

The diagnosis of congenital CMV infection should be made by the detection of virus in body fluids (urine or saliva are recommended) during the first 3 weeks of life.

As over 90% of newborns with congenital CMV infection are asymptomatic at birth, they will not be diagnosed unless newborns are screened. Screening for congenital CMV infection can be accomplished accurately by testing saliva or urine for virus although universal screening cannot be recommended until data supporting cost-effectiveness are available.

Although isolation of CMV from urine or saliva is the gold standard for diagnosis or screening, PCR detection should work well for diagnosis but it has not been adequately evaluated for screening purposes.

Follow-up

Infants and children with congenital CMV infection should have audiological evaluations at least twice per year for the first 3 years of life and annually up to school age because of the risk of progressive and late onset hearing loss.

Every infant with congenital CMV infection should have at least one fundoscopic examination for retinal lesions. If lesions are present, the follow-up examinations are recommended at least annually.

Infants and children with congenital CMV infection should receive services aimed at maximizing their hearing, speech, vision, cognitive and motor functions if any impairments are found.

Treatment and prevention of congenital CMV infection

Ganciclovir

In a Phase II trial, ganciclovir therapy led to a transient reduction in the overall quantity of CMV in the urine and other sites. Neutropaenia, thrombocytopaenia and elevated values for liver function tests were observed in a significant number of children, and required dose modification. Nevertheless, most children completed the 6-week treatment course.

The mortality rate was as low or lower than in historical trials. Moreover, the percentage of study children who were developing normally was in excess of that anticipated from the

literature. Hearing improvement or stabilization occurred in 16% of infants at 6 months or later. These improvements are notable as the children enrolled in the study had severe congenital CMV disease. However, this Phase II investigation was insufficient to draw definitive conclusions as to the therapeutic efficacy of antiviral therapy in the management of infants with symptomatic congenital CMV disease. Ganciclovir has also been studied in 12 children with CMV infection but, although encouraging, the sample size was too small to allow conclusions regarding efficacy to be drawn.

Currently, no antiviral treatment for congenital CMV infection has been shown to decrease the frequency or severity of CNS damage in controlled clinical trials. It is possible that the use of ganciclovir in some newborns with cytomegalic inclusion disease could decrease mortality or severe morbidity in the newborn period though this has not been demonstrated in controlled clinical trials.

Compassionate use of ganciclovir in newborns with life-threatening or vision-threatening congenital CMV infection is probably justified.

In utero treatment

Pre-clinical studies of benzimidazole ribonucleosides suggest that they hold promise for the treatment of maternal and congenital CMV infection. They have a potent anti-CMV effect, a favourable toxicity profile and good oral bioavailability.

There is currently no method of proven efficacy for preventing maternal CMV infection during pregnancy.

Vaccination

At present, there is no licensed CMV vaccine and none has been specifically tested in pregnant women. Several candidate vaccines are under development.

Behavioural intervention

It is likely that hygienic precautions (e.g. frequent handwashing after contact with young children) will not be sufficiently effective to prevent acquisition of CMV infection by seronegative women.

Research initiatives

The following initiatives are required:

- Development of a vaccine to prevent maternal and congenital CMV infection
- Development of antiviral therapy which can be used safely in pregnant women with primary CMV infection to prevent transmission of virus to the fetus
- Development of antiviral therapy which can be used pre-natally to treat the infected fetus
- Development of antiviral therapy which can be used safely in newborns and infants with congenital CMV infection to decrease the frequency and severity of impairments of hearing, vision, cognitive and motor functions.

Epidemiology and Natural History of Varicella in Pregnancy

Geographical Differences in the Incidence of Varicella

In immunocompetent populations, the epidemiology of varicella zoster virus (VZV) infection differs between tropical and temperate countries. In temperate countries, most primary infections occur before 10 years of age. This is demonstrated by age-specific seroprevalence of VZV in the USA, UK (Figure 1) and Germany which increases sharply in young children and after the age of 15 years, less than 10% of individuals remain susceptible to VZV infection.[228–231]

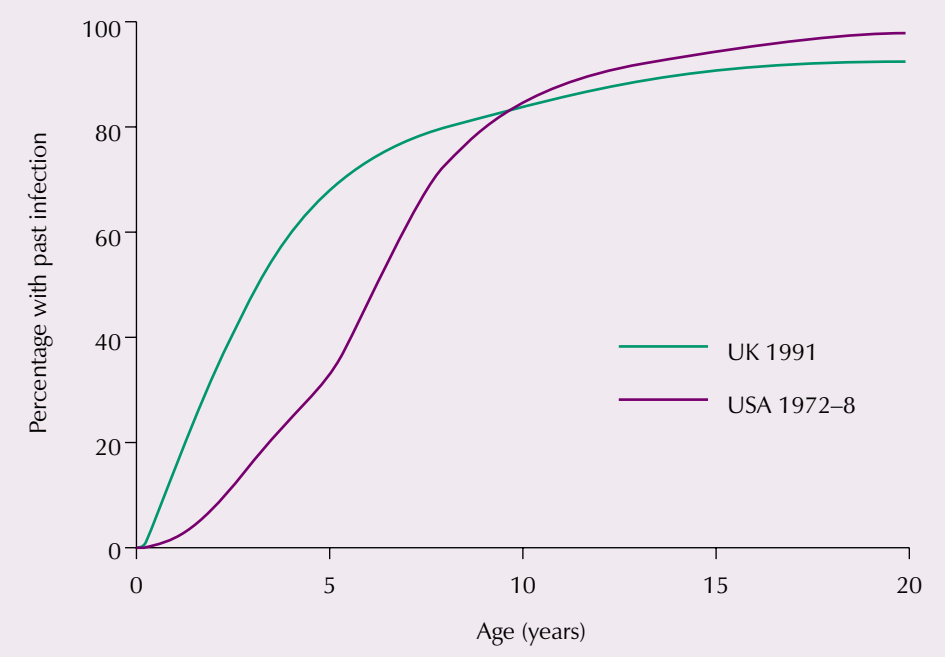

Figure 1: Cumulative age-specific incidence of seropositivity to VZV[228]

There can be epidemiological differences between temperate countries. For example, in Scotland where varicella has been a notifiable disease since 1988, 20% of cases are in those of 15 years or older,[232] whereas among cases reported to the Massachusetts Department of Health from 1952 to 1961, only 2.6% were in this age group.[233] Later statistics from three reporting areas in the USA (Massachusetts, Illinois and New York City) demonstrate a mean percentage of 5.1% cases in this age group in the period 1972–1978. The differences between Scotland and the USA may partly reflect true differences in the age distribution of varicella. Age-specific consultation rates will influence the age distribution of cases reported by physicians, and the patterns of consultation may vary in countries with different primary healthcare systems. These substantial differences may also reflect a recent increase in the proportion of cases of varicella in adults, especially as the UK data were collected up to 30 years later than the USA data.[228]

In comparison with temperate countries, primary VZV infection is apparent much later in life in tropical countries, with peak seroprevalence only being reached in adults over 40 years of age. Retrospective analyses of seroprevalence studies from the mid-70s and early-80s show that the mean age of infection in most tropical countries is over 20 years of age and that the overall VZV seroprevalence in those over 15 years of age appears to be low (41–72%) compared with that found in temperate climates.[234] In countries with intermediate climates,

the seroprevalence of VZV appears to fall between the two extremes. For example, in Nepal, the overall seroprevalence in adults is about 80%, between that found in St Lucia (60%) and the USA, Japan or Europe (95%).[235]

The differences in the age-distribution of varicella in different countries means that individuals from low endemicity countries (low seroprevalence of VZV) may be considered high-risk groups for acquisition of varicella when they emigrate to countries of high VZV endemicity.

Change in the age of infection

The mean annual rate of varicella infection in the UK is estimated to be about 600 cases per 100 000 people which is approximately the same as the birth rate. The same is true in the USA, but some recent studies in the UK and USA suggest that the mean age of acquiring varicella may be rising, with an increasing trend in the number of cases occurring in adults.[236–238]

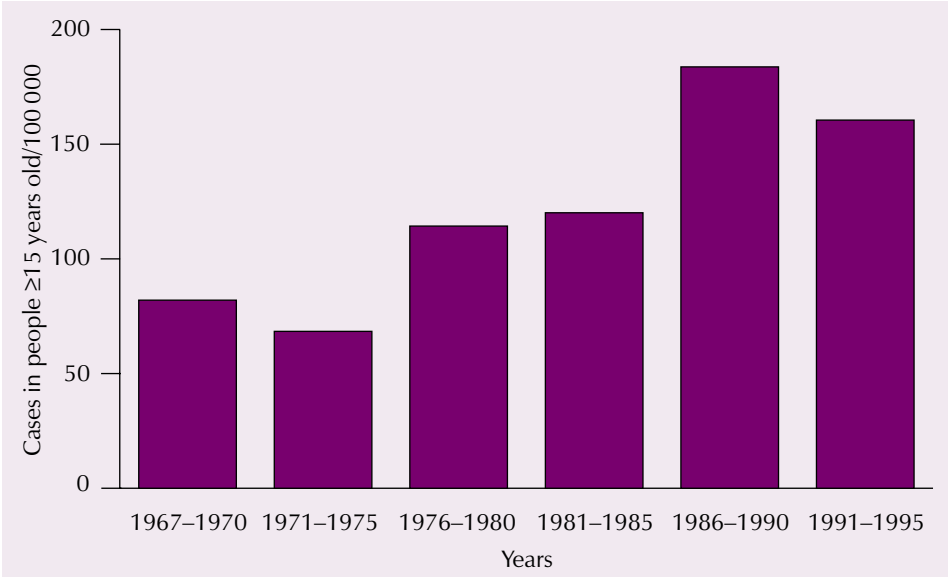

Figure 2: Varicella cases in persons 15 years or older reported in England and Wales[228]

In England and Wales, surveillance data show an increase both in the proportion of varicella cases and in the consultation rates in the past 25 years for persons 15 years or older, with a plateau (Figure 2) in the 1990s.[228] The proportion of cases in this age group rose from 6.9% in 1967 to 20.0% in 1995; the consultation rates for varicella in 15–44-year-olds showed a 2.3-fold increase, from an average of 118 per 100 000 between 1967 and 1970 to 272 per 100 000 between 1991 and 1994.[228] It is unlikely that the reported change in the age distribution of varicella results from these changes in the age-specific consultation rates as varicella mortality rates also rose over the same period.[228]

Similar trends have emerged from a study in the USA which reported an increase in hospitalizations due to adult varicella among military recruits.[236] Hospital records for 10 687 adult varicella admissions were reviewed and showed an 18-fold increase among naval recruits in the number of admissions from 1975 to 1988 and a four-fold increase between 1980 and 1988 among army personnel. Of these cases, 57% were in those aged 17–20 years, suggesting an increase in the VZV susceptibility of the young adult population.[236] Earlier reports recorded an increase in the average proportion of cases in persons 15 years or older from 2.6% in 1952–1961 (cases reported to Massachusetts Department of Health) to 5.1% for 1972–1978 (cases reported in Massachusetts, Illinois and New York City).[233,239] Studies in USA military personnel have also revealed that individuals from tropical countries are more likely to be seronegative[240,241] and at greater risk of hospitalization from the complications of varicella.[242]

A change in age distribution has not occurred in all countries. For example, in Japan, comparison of two seroepidemiological surveys in 1973 and 1984 does not reveal any evidence of a major change in epidemiology.[243] The reasons for the apparent shift in age distribution in the USA and UK are unclear, but it is unlikely to have resulted from immigration of susceptible adults from tropical countries as, in the UK, the number of immigrants would not have been sufficient to account for the observed changes.[228]

If this epidemiological change in the age of VZV infection proves to be substantiated, then it will have important implications for future morbidity and mortality and for infection in pregnant women.

Epidemiology of Varicella in Pregnancy

In North America, an estimated 6% of varicella cases occur during childbearing age,[244] although only 0.05–0.07% of pregnancies are complicated by VZV infection.[245] In the UK, it has been estimated that 0.3% of gestations are associated with VZV infection.[238]

Herpes Zoster in Pregnancy

Herpes zoster in old age reflects the inability of the host to mount a specific cellular immune response to VZV. There is, however, no consistent evidence that herpes zoster occurs more frequently in later pregnancy due to the waning of VZV-specific immunity. In a study of 14 women, nine (64%) developed herpes zoster during the third trimester as compared with only one (7%) in the first trimester.[246] In comparison, another study of 366 (pregnant) women reported that herpes zoster occurred with almost equal frequency in each trimester.[247]

Complications of Varicella

Children and non-pregnant adults

The complications of VZV infection are rare in immunocompetent children with less than two reported deaths per 1 000 000 cases in those aged 1–14 years.[248] Varicella-associated complications and deaths are more frequent in adults. The most common serious complication of varicella is pneumonia with up to 30% of adults having some evidence of pulmonary involvement.[237,238,245,249] Its severity ranges from a mild illness to life-threatening disease characterized by cough, tachnypea, dyspnoea, haemoptysis, chest pain and cyanosis. Typical radiographical changes include diffuse, peribronchial infiltrates. Other manifestations of disseminated disease occur less frequently. The greater mortality associated with VZV

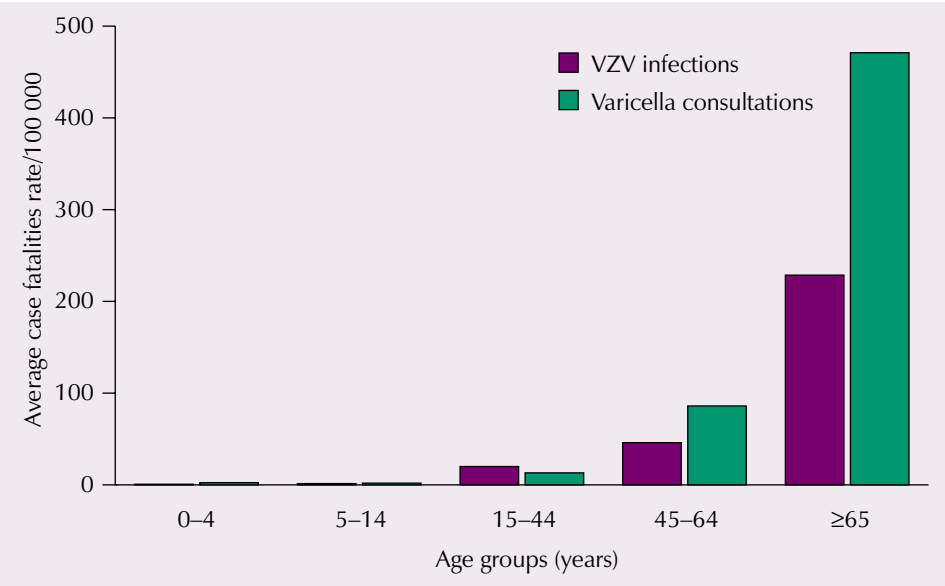

Figure 3: Age-related mortality associated with VZV infection[228]

infection in adults is illustrated by a recent study that documented that less than 5% of VZV cases were in those older than 20 years but 55% of varicella-related deaths were in this age group.[250] As age increases, there is a steep rise in mortality resulting from VZV infection (Figure 3),[228] which, combined with the shift in age distribution of VZV infection would suggest that there would be an increase in varicella-related mortality. In the UK, there has been an increase in the proportion of adult deaths due to varicella; in 1967, 42% of all deaths attributed to varicella were in persons aged 15 years or older, compared with 87% in 1994.[228]

Pregnant women

The main risk to women who acquire VZV infection during pregnancy, as for other adults, is varicella pneumonia.[237,238,249] When varicella pneumonia occurs in pregnancy, the mortality rate may be as high as 40% in the absence of antiviral therapy.[237,238,249]

Anecdotal evidence suggests that pregnant women may be at greater risk from developing severe varicella and its complications than non-pregnant women of the same age, and that life-threatening pneumonia occurs more frequently.[246,251,252] A study of 43 pregnant women with varicella documented other maternal effects; nine women (20%) had varicella-associated morbidity (pneumonia, premature labour, premature delivery, herpes zoster) and one woman died.[246]

Fetal infection (early pregnancy)

Intra-uterine VZV may occur irrespective of the severity of the infection in the mother. Haematogenous spread of virus across the placenta is the main route for congenital infection.

VZV infection during early pregnancy can result in a range of congenital defects referred to as the congenital varicella syndrome (Table 1). Although it was initially thought that congenital varicella syndrome occurred only in the first trimester, approximately half of the recorded cases in one study developed when the mother had varicella in the second trimester.[253] Thus, the risk of congenital varicella syndrome after maternal infection extends throughout the first half of pregnancy.

Congenital defects associated with VZV infection	
Skin	Scarring
Limb	Hypoplasia of bone and muscle
Central nervous system	Microcephaly, mental retardation, sphincter dysfunction
Eye	Cataract, chorioretinitis, microphthalmia

Table 1: Clinical characteristics of congenital varicella syndrome

It is difficult to obtain precise estimates of the risk of congenital varicella syndrome. In a prospective, case-controlled study by Pastuszak *et al.*,[254] the pregnancy outcomes of 106 women with clinically diagnosed VZV infection in the first 20 weeks of pregnancy were compared with 106 unexposed, age-matched controls. Only one in 86 live births (1.2%) in the varicella group had features of congenital varicella syndrome (Table 1). When these results were pooled with those of four previous studies the mean risk was estimated to be 2.2%.

These findings were corroborated by a larger, uncontrolled study of 1373 pregnant women exposed to VZV in the first 36 weeks of pregnancy. In this study, the overall incidence of congenital varicella syndrome was 0.7% but the risk varied according to time of infection. Congenital varicella syndrome occurred in seven out of 351 (2%) infants whose mothers developed varicella infection between weeks 13 and 20 of gestation, in two out of 472

Fetal risk*		
First trimester	**Second trimester**	**Third trimester**
2/27 (7.4)	0/32	2/76 (2.6)[255]
0/23	0/8	0/2[256§]
1/11 (9.0)	0/11	0/16[246]
0/35	NG	NG[257]
2/472 (0.4)	7/351 (2.0)	0/477[247]
–1/86 (1.2)[†]	0/14[254]	
3/107 (2.8%)[‡]	NG	NG[258]

**Ratio of the number of infants with congenital varicella syndrome compared with the total number of live-born infants*
NG=Not given
[†]Estimated risk for mothers infected in the first 20 weeks of pregnancy; [‡]Risk for mothers in first 24 weeks of pregnancy
[§]Figures also included in reference 247

Table 2: Pooled results from prospective studies measuring fetal risk after maternal VZV infection during pregnancy

(0.4%) whose mothers were infected during weeks 8–13 and in none of 477 pregnancies in which maternal infection was acquired after week 20 (Table 2).[247] A smaller study with 107 women who contracted varicella before 24 weeks of pregnancy recorded a risk of congenital varicella syndrome of 2.8%.[258] Thus, this potentially serious consequence of maternal VZV infection has a relatively low risk (2%), with the greatest risk when maternal infection occurs during weeks 8–20 of gestation.[247,254]

The study by Pastuszak and colleagues[254] found no difference between the infected and uninfected women in the number of live births, miscarriages or elective terminations. There was a trend toward more pre-term deliveries in the varicella group (14.3% versus 5.6%; $P=0.05$) but gestational age at delivery and birth weights were similar.[254] Maternal varicella infection at any time during pregnancy can result in herpes zoster in the infant.[259]

Neonatal infection (late pregnancy)

Varicella in the newborn can occur if the mother becomes infected 3 weeks before delivery. As with infection earlier in pregnancy, transplacental virus transmission is the usual route of infection although contact with maternal lesions during or after delivery may also lead to neonatal infection.

The severity of varicella in the neonate is largely dependent on the time of onset of maternal illness in relation to delivery. The usual interval between onset of rash in the mother and onset in the neonate is 9–15 days. Neonates are at highest risk of developing varicella when maternal varicella begins between 5 days before and 2 days after delivery[260,261] leading to the appearance of symptoms in the neonate 5–10 days after birth. Approximately 20% of infants born in the high risk period (5 days before until 2 days after birth) will have symptomatic neonatal varicella, with disseminated infection and visceral involvement.[262] The most common life-threatening complication is pneumonia and untreated neonatal varicella is associated with a mortality rate as high as 30%.[256,263] For mothers with varicella during the perinatal period, the incidence of neonatal varicella was reported to be 48%.[260] For the neonates infected outside the high-risk period, the disease is generally mild with few vesicles.[237,238]

The high-risk results from a lack of transplacental transfer of maternal antibody despite transmission of VZV to the neonate. If the mother has varicella more than 7 days before delivery, the neonate invariably has antibodies as there is sufficient time for maternal immunoglobulin to be produced and cross the placenta.[260] However, neonatal varicella may occur despite the presence of maternal antibodies to VZV.[264]

Impact of maternal herpes zoster on the neonate

There appears to be very little risk to the fetus or neonate from maternal herpes zoster during pregnancy[246,247,260] or at delivery.[247] The majority of infants delivered to women with herpes zoster have normal development and no adverse sequelae,[265] although there are sporadic reports of maternal herpes zoster associated with congenital complications.[266] The reason for the low risk associated with maternal herpes zoster may be the presence of passively acquired antibody in the neonate from the mother's pre-existing humoral immunity to varicella. However, it has been suggested that infants born with abnormalities after maternal herpes zoster should be investigated for virological and serological evidence of congenital varicella zoster infection.[247]

Neonatal herpes zoster

Herpes zoster in the newborn is rare. The condition is usually benign as pain does not seem to be a feature of such cases. It typically resolves without sequelae or further recurrences[237,238] and there is no need for treatment with antivirals.

Conclusions

VZV can cause serious infection in the pregnant woman. If acquired during the first half of pregnancy, it can result in congenital varicella syndrome. Varicella infection of the newborn can be life-threatening if the infant is delivered 5 days before to 2 days after the onset of maternal illness.

Management approaches for VZV infection should be based on the understanding that the risk from varicella to both the fetus and neonate or newborn is greatest in seronegative women. Similarly, an assessment of the risk of congenital varicella syndrome can help determine approaches to its identification. As the risk of congenital varicella syndrome is only 2%, the diagnostic method used must have a lower risk to the fetus or neonate.

Summary

The epidemiology of VZV infection differs between temperate and tropical countries. In temperate countries, peak seroprevalence occurs in adolescents whereas in tropical countries peak seroprevalence is achieved only in adults over 49 years of age. Thus, individuals from areas of low endemicity who emigrate to areas of high endemicity are susceptible to infection as adults.

In North America, an estimated 6% of varicella cases occur during child-bearing age, whereas it has been estimated that 0.3% of gestations are associated with varicella infection in the UK.

The mean age at which VZV infection occurs appears to be rising with an increasing number of VZV infections in adults. If this epidemiological change is substantiated, then it will have important implications for future morbidity and mortality among the general population and among pregnant women.

The main risk to women who are infected with varicella during pregnancy is varicella pneumonia. The mortality rate of untreated varicella pneumonia is 40%.

Fetal infection in the first half of pregnancy can result in congenital varicella syndrome, but does not appear to increase the risk of prematurity or low birth weight. The defects due to congenital varicella include skin scarring, limb atrophy and central nervous system abnormalities. The risk of congenital varicella is approximately 2%.

Neonates are at high risk of developing varicella when maternal varicella begins between 5 days before and 2 days after delivery. The high risk is the result of transmission of VZV *in utero* before the fetus has acquired varicella antibodies by transplacental transfer. The most common life-threatening complication is pneumonia.

Management of Varicella Zoster Virus Infection in the Pregnant Woman and Neonate

Diagnosis in the Pregnant Woman

A history of previous varicella zoster virus (VZV) infection is generally accepted as proof of immunity. In a study of staff in a children's hospital, only 0.9–3.2% of those who recalled having varicella were non-immune.[267] Among subjects with no or uncertain prior exposure to VZV, only 10–36% were non-immune.[267,268]

The diagnosis of VZV infection is usually suspected from clinical presentation and, although laboratory tests are not routinely required, they may be useful for confirmation. VZV can be isolated from vesicular lesions in the first 3–4 days after onset. In certain settings (e.g. hospitals), the diagnostic test of choice is to stain scrapings from vesicles with fluorescein-conjugated monoclonal antibodies to varicella antigens expressed on the surface of infected cells. This technique is rapid, reliable and relatively inexpensive.[269] Acute infection can also be confirmed by serological testing shortly after the onset of rash and the detection of VZV-specific immunoglobulin (Ig) M and IgG antibodies in rising titres during the following 2 weeks.

The presence of IgG antibodies in the serum in the absence of symptoms indicates previous infection, allowing women to be reassured of the lack of risk of VZV infection to themselves and their unborn child. However, particularly with equivocal or low IgG titres, asymptomatic re-infection can occur as second attacks of varicella.[264]

Indications for serological testing

Serological testing should be performed when it can be done in a timely fashion, especially if passive prophylaxis is being considered and the immune status of the mother is in doubt. Such testing can be conducted with enzyme immunoassay (EIA), fluorescence antibody to membrane antigen (FAMA) technique or, when a very rapid result is needed, the latex agglutination test (LA).[270] EIA, which is currently the most widely used method, is based on a whole cell extract of VZV antigen and, therefore, has the disadvantage of cross reactivity with herpes simplex virus (HSV) and cytomegalovirus (CMV), albeit at very low rates. Therefore, glycoprotein-specific ELISAs (gp ELISAs) that use purified VZV antigens (gE, gB and gH) are under development. These gp ELISAs appear to be highly specific for VZV with no cross reactivity with HSV-1, HSV-2 and CMV. Moreover, in comparison with a commercial total antigen ELISA (VARELISA), they are more sensitive.[271,272]

Antigen detection and virus culture

Virus detection is usually reserved for complicated varicella. Virus culture is less sensitive than direct antigen staining as the virus is highly cell-associated in tissue culture and is not released in high titres into the overlying medium. Moreover, cytopathic effects develop slowly in tissue culture (in 10–14 days), and, consequently, results are not available soon enough to be clinically useful.[269] Since the early 1990s, one diagnostic method of value is detection of VZV DNA by polymerase chain reaction (PCR), but there are no commercial tests currently available.

Pre-Natal Diagnosis

Pre-natal diagnosis of congenital varicella syndrome following maternal primary VZV infection may allow the woman to make an informed choice about termination of pregnancy.[258] A complicating factor is that the diagnosis of intra-uterine VZV infection is difficult, and even if made, the effect of infection is unclear as it does not usually equate with damage.[258,273–275] Importantly, the diagnostic techniques used – amniocentesis and cordocentesis – are not

completely safe. Their rates of fetal loss vary according to the experience of the investigator, the gestational week of performance and the condition of the fetus. For cordocentesis performed between 18 and 24 weeks of gestation, the risk of fetal loss is estimated to be 0.8–1.5%,[276] and amniocentesis performed between 15 and 22 weeks of gestation is associated with a fetal loss rate of 0.2–1%.[277] In another study, amniocentesis conducted after 16 weeks of gestation was associated with a 1.7% rate, whereas the background rate of fetal loss was 0.7%.[278] A separate randomized study has shown that amniocentesis early in the first trimester (before 13 weeks of gestation) is associated with a higher rate of fetal loss (7.6%) than after 15 weeks of gestation (5.9%).[279]

From currently available experience in pre-natal diagnosis, amniotic fluid taken at 18–23 weeks of gestation and 4–6 weeks after onset of maternal varicella yields the best results for detection of fetal infection. Caution is required in interpreting the findings as a positive result is not predictive of fetal abnormalities in the absence of suspicious findings by ultrasound. Therefore, ultrasound screening between 19 and 23/24 weeks of gestation may be advised for women with varicella infection in the first 21 weeks of pregnancy. If the sonographic findings are abnormal, fetal blood and amniotic fluid obtained in the 22–23 weeks of gestation should be tested for VZV DNA as VZV-specific IgM is rarely detected in fetal blood.[258,275,280,281]

In summary, as the risk of congenital varicella syndrome is low (1–2%), the risk associated with amniocentesis or cordocentesis suggests that they are unlikely to be widely used diagnostic tools for detection of congenital varicella syndrome.[282]

Diagnosis in the Newborn

The diagnosis of varicella in the newborn is usually based on clinical findings. Clinical illness typically develops 5–10 days after delivery. However, the clinical course of varicella can vary in progression and severity. Some infants have only scattered lesions and no systemic signs of illness whereas others may have a biphasic course with cutaneous eruptions followed by dissemination. In others, extensive skin lesions and visceral involvement may accompany the acute illness.

Management

Pre-exposure prophylaxis in the pregnant woman

Vaccination safety and efficacy

The development of the live-attenuated varicella vaccine offers the potential for effective pre-exposure prophylaxis. The varicella vaccines licensed in the USA, Japan and Korea are composed of the Oka strain of live-attenuated VZV. The vaccine is currently not licensed in the UK[283] or other European countries, although it is available on a compassionate basis. Clinical studies have demonstrated that varicella vaccination is both safe and effective.[284–287] However, only one placebo-controlled study has been conducted and it was among children 1–14 years of age. In the trial, 468 children were immunized with a dose of 17 430 plaque forming units (pfu) of virus and 446 were given placebo.[287] The vaccine efficacy was 100% over 9 months and 91% in the placebo group. In the second year of the study, one vaccinated child developed varicella, giving an efficacy rate of 98%.[287] Over a 7-year follow-up period, the efficacy of the vaccine was estimated at 95%. The vaccine was well tolerated, although it was at a much higher titre much higher than commercially produced vaccines.[287] A placebo-controlled trial has not been conducted in adults.

Data from all American trials of Varivax (Merck & Co. Inc.) in which vaccinated individuals of all ages were followed up for up to 9 years demonstrated efficacy of 95.6–99.0% per year depending on vaccine lot and time since vaccination.[288] Trials, in which there were no placebo controls, have demonstrated that vaccination significantly lowers the attack rate among household exposures in adults and children,[289,290] and those breakthrough infections which do occur are milder than wild-type infection in unvaccinated individuals (Table 1).[289]

Study group	Follow-up (years)	Rash or fever (%)	Seroconversion (%)	Protection 1–3 years (%)	Protection >3 years (%)
Children	2–16	5	95	89–94	88
Adults		10	>90 (two doses)	70	86

Table 1: Clinical trials with varicella vaccine[289]

Varicella vaccination is generally well tolerated in healthy adults and children (Table 1). In healthy children, the frequency of rash after immunization is approximately 5% and there are very few skin lesions.[253,286] Other common adverse events include fever (15%), temporary discomfort at the injection site (19–24%) and rash at the injection site (3–4%).[253,286] Similar adverse event rates are seen in healthy adolescents and adults, in whom two doses of vaccine are required. However, the rate of vaccine-associated rash in adults (10%) is twice that seen in healthy children.[253]

Varicella vaccination recommendations

Vaccination of seronegative women of child-bearing age who are not pregnant should be considered. The *US Advisory Committee on Immunization Practices* (ACIP) has strengthened its recommendations for varicella vaccination of susceptible individuals older than 13 years.[291] Among high-risk groups, vaccination is *recommended* for susceptible, non-pregnant women of child-bearing age. The previous recommendations stated that this group should be *considered* for vaccination.[288]

Pregnancy is mentioned among the contraindications for varicella vaccination. No epidemiological data are available about exposure to the vaccine during pregnancy and the effects on the fetus are unknown. A theoretical risk is that a vaccinated woman may develop varicella infection from the attenuated virus with the consequence of fetal varicella infection. Therefore, the Varivax manufacturer advises a 3-month interval between vaccination and conception, although the ACIP and *Centers for Disease Control* (CDC) advise that non-pregnant women who are vaccinated should avoid becoming pregnant for 1 month following each injection of vaccine.[288,292] However, inadvertent vaccination just before or early in pregnancy is not a justification for termination of gestation. In the USA, a *Varivax Pregnancy Registry* (telephone: ++1 800 986 8999) has been established to monitor the maternal and fetal outcomes of pregnant women who receive varicella vaccine 3 months before and at any time during pregnancy.

Post-exposure prophylaxis in the pregnant woman

The aim of post-exposure prophylaxis is to prevent or modify maternal illness in the susceptible woman and to reduce the risk of intra-uterine VZV infection. It should be offered to susceptible pregnant women (with significant exposure, e.g. from their own family) during the first 20 weeks of gestation, because secondary cases may be more severe and there is a 1–2% risk of congenital varicella in their infants.[247]

Before administering post-exposure prophylaxis, it is important to ascertain the type of VZV exposure and the previous varicella history of the pregnant woman. If there is any uncertainty about infection history, antibody status should be determined rapidly.

The available options for post-exposure varicella prophylaxis are but not all may be suitable for pregnant women:

- Passive immune prophylaxis with varicella zoster immune globulin (VZIG)
- Antiviral therapy
- Vaccination during the incubation period.

VZIG

Although the purpose of VZIG administration in early pregnancy is principally the prevention of maternal VZV infection, the attenuation of the disease is also considered valuable. In various studies it has been shown that the protective efficacy of VZIG differs depending on the IgG antibody concentration of the various formulations.[260,293]

In the UK, two VZIG preparations (UK VZIG) are available for intramuscular (im) administration and are distributed by the Public Health Laboratory Service. The preparations have a relatively low IgG antibody concentration (approximately 700 IU per adult dose) and their effect is to attenuate disease rather than to prevent infection.[238] A substantial proportion (15%) of high-risk, non-immune infants and children exposed to varicella who have received UK VZIG[294] develop subclinical infection, as detected by testing for seroconversion in blood taken 1 month post-exposure.

VZIG preparations for intramuscular application are also available in the USA (approximately 625 IU per adult dose).[288] The protective efficacy of USA VZIG in the adults is approximately 70% (Enders, personal communication).

In Germany, two commercial preparations of VZIG with an IgG antibody concentration of approximately 2100 IU per adult dose are available; one is for im administration and the other is for intravenous (iv) use. Neither of these offer complete protection against varicella. In a study of 212 seronegative pregnant women, VZIG was given in the recommended dosage either im (e.g. for a 70 kg woman: 2100 IU) or iv (e.g. for a 70 kg woman: 1750 IU) and within 1–3 days of significant exposure. However, 41% of the women had clinical varicella, either normal or modified disease, whereas a further 5% had subclinical infection (Table 2).[247]

VZIG administration following days after exposure	Total	Outcome					
		No infection		Subclinical infection		Modified/normal varicella	
	(n)	*(n)*	*(%)*	*(n)*	*(%)*	*(n)*	*(%)*
1–3 days	153	83	(54)	7	(5)	63	(41)
4–5 days	46	27	(59)	1	(2)	18	(39)
6–10 days	13	4	(31)	3	(23)	6	(46)
Total	212	114	(54)	11	(5)	87	(41)

IgG and IgM antibodies were determined with the ELISA Enzygnost Anti VZV IgG-IgM in the initial and follow-up sera

Table 2: Outcome of varicella exposure of 212 seronegative pregnant women following administration of VZIG[247] (Enders, personal communication)

VZIG should be administered as soon as possible to susceptible (seronegative) women following exposure to VZV in the first 20 weeks of gestation. VZIG prophylaxis for women exposed later in pregnancy to reduce the risk of varicella is a lower priority.[237,247,256,281,293,295,296]

There is limited evidence that VZIG benefits the fetus and reduces the risk of intra-uterine varicella infection.[247,297] In a prospective study of 97 pregnant women who contracted varicella despite receiving VZIG, there were no cases of congenital varicella syndrome, and VZV-specific IgM antibodies were detectable at birth in only one infant (maternal varicella in week 36 of gestation).[247] This study did not document a statistically significant protective effect of VZIG.[298] In another prospective study, 5% of 106 varicella-infected women received VZIG after exposure in early pregnancy.[254] The only infant with congenital varicella syndrome was born to a woman who received VZIG. The VZV-susceptible mother received VZIG 4 days after her exposure to varicella at week 11 of pregnancy; she developed varicella 2 weeks later. These

two studies demonstrate the need for a large prospective trial to clarify whether passive prophylaxis can prevent congenital varicella syndrome.

Antiviral therapy

Clinical studies in children indicate that post-exposure prophylaxis with oral aciclovir may be effective in reducing the severity of varicella. In a placebo-controlled trial of oral aciclovir (40 or 80 mg/kg/day for 7 days started 7–9 days after exposure but before onset of rash) in children exposed to varicella and examined 14 days post-exposure, development of clinical varicella did not occur in 21 of 25 treated children but developed in all 25 untreated children.[299] In another study in which children were given oral aciclovir 1–3 days after exposure, 10 out of 13 children developed varicella within 28–42 days.[300] The data suggest that post-exposure prophylaxis is less effective if administered too early in the incubation period. However, the studies were performed in different populations who received different doses of aciclovir and were followed up for different lengths of time. This strategy for post-exposure prophylaxis is currently not advocated for pregnant women, at least not during the first 20 weeks of pregnancy.

In pregnant women, the potential benefits of treatment should be balanced against potential fetal adverse outcomes. Although aciclovir is not licensed for use in pregnancy, the prospective follow-up of a total of 1207 women treated during the first ($n=739$), second ($n=188$) and third ($n=278$) trimesters did not show an increase in the number of birth defects when compared with those expected in the general population.[78,79] In addition, there is no consistent pattern of defects among prospective or retrospective aciclovir reports. Although the data are not strong enough to exclude a teratogenic effect of aciclovir, this drug should not be withheld in early pregnancy if clinically indicated.

Vaccine

Studies in the USA and Japan suggest that varicella vaccine can prevent or modify the severity of the disease if used within 3 days, and possibly up to 5 days, following exposure.[301–303] In the USA, the ACIP has recommended the use of varicella vaccine for post-exposure prophylaxis and outbreak control.[291] Active prophylaxis with vaccine is not advocated for women in pregnancy, but it may be of value for non-pregnant women of child-bearing age.

Management of the Pregnant Woman with Varicella

Recommendations for treatment of varicella in adults with oral aciclovir, including pregnant women with a normal course of illness, differ in various countries. In the UK and Australia, oral aciclovir for 7 days (800 mg five times daily) is offered to people including pregnant women over 20 weeks of gestation presenting within 24 hours of rash onset. This procedure is known to reduce the severity of disease in non-pregnant adults,[288,304–306] but no studies have prospectively assessed the efficacy of antiviral therapy in pregnant women. A retrospective analysis of aciclovir in pregnant women with varicella pneumonitis noted reduced morbidity and mortality when varicella infection occurred during the last two trimesters; aciclovir reduced mortality rates to 14% compared with 41% in untreated historic controls.[249]

As the complications of varicella are more common in adults, given the limited Pregnancy Registry data available, there is no apparent reason to withhold aciclovir at any time during pregnancy. The dosage and route of administration are determined by the severity of disease. If a woman has severe or complicated disease (e.g. pneumonitis), iv aciclovir should be given (10 mg/kg every 8 hours for 7 days or longer). Pregnant women with less severe disease should be treated with oral aciclovir (800 mg five times per day for 7 days or longer). More data are required on long-term follow-up of children exposed to aciclovir *in utero*. The roles of valaciclovir and famciclovir for the treatment of varicella infection remain to be evaluated in clinical trials.

The pregnant woman with varicella should avoid contact with all other pregnant women and neonates until her lesions are crusted.

Post-Exposure Prophylaxis in the Neonate

Administration of VZIG to the infant is advised if the mother develops varicella 7 days before or after delivery. The neonate of a mother with active varicella should be isolated while in hospital, from birth to day 21 (or day 28 if the infant has been given VZIG).

Despite VZIG prophylaxis, approximately one-half to two-thirds of infants exposed to maternal varicella around the time of delivery will become infected.[237] Although in most cases the infection is mild, fatal outcomes in VZIG-treated infants have been reported in those whose mothers developed varicella rash in the period 4 days before to 2 days after delivery.[307–309] In the UK, VZIG is also recommended for infants with non-maternal post-natal exposure during the first 7 days of life and who are without VZV antibody.

VZIG does not appear to reduce the infection rate for varicella in neonates although it may reduce the risk of serious infection. In a study in which VZIG was administered to 41 neonates born to women whose varicella lesions began 4 days before to 2 days after delivery, the neonatal attack rate was 51% despite VZIG therapy.[310] There were no fatalities and only two cases of severe disseminated varicella. In a larger UK study of 280 infants born to mothers with varicella or herpes zoster in the perinatal period and who received VZIG, the attack rate was 48%, with the infection being severe in 19 infants.[260]

At present, there is no convincing evidence as to whether mothers who develop varicella in the high-risk period around the time of delivery should be isolated from their infants or allowed to breast feed.[311] Neonates whose mothers develop varicella shortly before delivery may have already been infected by transplacental transfer of virus at the time of birth. For those infants whose mothers develop varicella in the perinatal period, transmission before rash onset is likely. Although one study has demonstrated VZV DNA by PCR in breast milk,[312] no evidence was provided for transmission of the infection to the newborn via breast milk. For women with lesions close to the nipple it is advisable to avoid direct contact with the infant and, if the mother wishes to breast feed, to give expressed milk from a bottle until the lesions have crusted.[313]

Neonates with congenital varicella syndrome do not need isolation from other children as they do not release virus.

Treatment of the Neonate

Neonates developing varicella should be observed closely. If they develop vesicles, they should be treated early with iv aciclovir. Occasionally neonates may develop varicella despite receiving VZIG. This is usually mild but therapy with aciclovir should be considered in these children.

Herpes Zoster in the Pregnant Woman and Neonate

In exposure to herpes zoster, passive prophylaxis is only recommended for VZV-seronegative women intimately exposed to patients with extensive herpes zoster lesions up to 21 weeks of gestation. Local guidelines for treating herpes zoster in adults should be followed. Women who develop localized herpes zoster in pregnancy should be reassured that the risk to the fetus is negligible. In addition, passive immunization of neonates whose mothers develop perinatal herpes zoster is not indicated.

Research Initiatives for Varicella

The duration of immunity conferred by varicella vaccine has not been clearly delineated and there is the possibility of seroreversion. The loss of immunity in older individuals would increase their risk of complications on exposure to wild type virus. It is, therefore, important to monitor seroreversion and evaluate the need for booster immunizations.

The neurodevelopmental effect of varicella *in utero* and herpes zoster early in life should be assessed.

Summary and Management Guidelines

Diagnosis

Pregnant woman

A history of previous VZV infection is generally accepted as proof of immunity. But, when it can be done in a timely fashion, determination of the immune status by ELISA is advisable before administration of VZIG.

The presence of IgG antibody in serum in the absence of symptoms indicates previous infection. The detection of IgM with a rising IgG titre in maternal serum indicates a recent infection.

VZV infection is generally suspected from clinical presentation, although laboratory testing may be required for confirmation. Serological testing is indicated when immunity to varicella must be determined, for example, when a past history is unreliable.

Pre-natal diagnosis

As the risk of congenital varicella syndrome is low (1–2%), the risk associated with the invasive pre-natal diagnostic methods, amniocentesis or cordocentesis, suggests that they are unlikely to be widely used diagnostic tools for congenital varicella syndrome.

Pre-natal diagnosis of congenital varicella syndrome following primary VZV infection can allow the woman to make an informed choice about termination of pregnancy.

Ultrasound screening between 19 and 23/24 weeks of gestation is recommended for all women with varicella in the first 21 weeks of pregnancy. If the sonographic findings are abnormal, fetal blood and amniotic fluid obtained at 22–23 weeks of gestation should be tested for VZV DNA. Testing for VZV-specific IgM in fetal blood is not helpful (*Category 2 recommendation*).

Diagnosis in the newborn

The diagnosis of VZV infection in the newborn is usually based on clinical findings. The clinical course of varicella in newborns can vary in progression and severity.

Pre-exposure prophylaxis – vaccination

The live-attenuated varicella vaccine, currently licensed in the USA, Japan and Korea, offers the potential for effective pre-exposure prophylaxis. Clinical studies have demonstrated that varicella vaccination is both well tolerated and effective.

Vaccination of VZV seronegative women of child-bearing age who are not pregnant should be considered (*Category 3 recommendation*).

The effects of the vaccine on the fetus are unknown, with no epidemiological information about exposure to the varicella vaccine during pregnancy. The manufacturer advises a 3-month interval between vaccination and conception, whereas the ACIP and CDC advise a 1-month interval.

Post-exposure prophylaxis in the pregnant woman

For susceptible, pregnant women with significant exposure to varicella during weeks 1–20 of gestation, post-exposure prophylaxis should be instituted.

VZIG

VZIG should be administered as soon as possible to the seronegative mother following exposure to VZV in the first 20 weeks of gestation, VZIG may be administered to the susceptible woman who is exposed to VZV in the third trimester to reduce the risk of varicella (*Category 2 recommendation*).

Antiviral therapy

Clinical studies in children suggest that post-exposure prophylaxis with antiviral therapy may reduce the severity of varicella. The value of post-exposure prophylaxis for the susceptible pregnant woman should be assessed in clinical trials (*Research need recommendation*).

Treatment of pregnant woman with varicella

If a woman is pregnant, the potential benefits of aciclovir should be balanced against potential fetal adverse outcomes. Although the data are not strong enough to exclude a teratogenic effect of aciclovir, this drug should not be withheld in early pregnancy if clinically indicated.

The complications of primary varicella infection are more common in adults. Given the limited Pregnancy Registry data available, there is no apparent reason to withhold aciclovir in pregnancy (*Category 2 recommendation*). The dosage and route of administration is determined by the severity of disease. The woman should be advised about the use of a drug unlicensed in pregnancy. More data are required on long-term follow-up of children exposed to aciclovir *in utero* (*Research need recommendation*).

If a woman has severe or complicated disease (e.g. pneumonitis) iv aciclovir should be given (10 mg/kg every 8 hours for 7 days or longer), (*Category 3 recommendation*). Pregnant women with less severe disease should be treated with oral aciclovir (800 mg five time daily for 7 days), (*Category 3 recommendation*).

The pregnant woman with varicella should avoid contact with all other pregnant women and neonates until her lesions have crusted.

Neonate

Post-exposure prophylaxis in the neonate

Administration of VZIG to the infant is advised if the mother develops varicella 7 days before or after delivery.

The neonate of a mother with active varicella should be isolated while in hospital from birth to day 21 (or day 28 if the infant has been given VZIG), whereas neonates with congenital varicella syndrome do not need isolation from other children.

Treatment of the neonate

Neonates with VZV infection should be observed closely. If they develop vesicles, they should be treated with iv aciclovir. Occasionally, neonates may develop varicella despite receiving VZIG. This is usually mild, but therapy with aciclovir should be considered.

Herpes zoster in the pregnant woman

Herpes zoster is not a risk to the fetus. Local guidelines for treating herpes zoster in adults should be followed.

Research initiatives for varicella

The duration of immunity conferred by the vaccine has not been clearly delineated and there is the possibility of seroreversion. The loss of immunity in older individuals would increase their risk of complications on exposure to wild type virus. Seroreversion in vaccinees should be monitored and the need for booster immunizations evaluated (*Research need recommendation*).

The neurodevelopmental effect of varicella *in utero* and herpes zoster early in life should be assessed (*Research need recommendation*).

As newer antivirals become available, their clinical efficacy in treating VZV-associated conditions in pregnant women and neonates should be evaluated (*Research need recommendation*).

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CHAPTER 5

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CHAPTER 6

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Appendix

Recommendation Categories

Category 1 Recommendation

Consistent evidence from controlled clinical trials. For example, for an antiviral this would be two properly randomized controlled clinical trials. In laboratory tests, consistent evidence from comparative studies.

Category 2 Recommendation

Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one centre), or from multiple time-series studies or dramatic results from uncontrolled experiments.

Category 3 Recommendation

Evidence from opinions or respected authorities based on clinical experience, descriptive studies or reports of expert committees.

Research Need Recommendation

Area in which research is warranted.

The *International Herpes Management Forum* (IHMF) Website, **www.ihmf.org** has information on the IHMF, forthcoming meetings and internet versions of *Management Strategies in Herpes* publications.

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