

Epidemiological, Clinical and Laboratory Aids for the Diagnosis of Neonatal Herpes – an Australian Perspective

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KEY WORDS

■ NEONATAL HERPES ■ EPIDEMIOLOGY ■ DIAGNOSIS ■ HERPES SIMPLEX VIRUS ■ PREGNANCY

SUMMARY

Neonatal herpes is rare in Australia, possibly because of the older average age at pregnancy compared with other developed countries, low herpes simplex virus (HSV)-2 seroprevalence in the general community, low risk of HSV-2 acquisition during pregnancy and relatively high HSV-1 seroprevalence in adults. Guidelines on herpes management in pregnancy have been produced by the Australian Society for Infectious Diseases and endorsed by the Australian College of Obstetricians and Gynaecologists. However, diagnosing and managing neonatal infection remains difficult. Until an effective strategy to prevent neonatal herpes is developed, our efforts should focus on improving early diagnosis of HSV disease in the neonate and developing more effective strategies to reduce early reactivation and long-term morbidity.

Introduction

NEONATAL HERPES IS uncommon in Australia, with rates estimated at 3.4–8/100 000 live births.¹ This is in marked contrast to the situation in parts of the USA, where the reported incidence is between 15 and 48/100 000 births.^{2,3} There are several possible reasons for this difference. First, recurrent genital herpes, which is most often caused by herpes simplex virus (HSV)-2, may be more common in adults (and consequently in pregnant women) in some parts of the USA than in Australia. Secondly, HSV-1 infection appears to be more common in Australian adults and this may confer some protection against subsequent HSV-2 infection. Finally, pregnant women in Australia may be at low risk of genital herpes acquisition during pregnancy compared with some American and European populations – a situation that appears to confer a high risk for the acquisition of neonatal herpes.²

HSV-2 Epidemiology: How Australia Compares

Nationally representative HSV-2 seroprevalence studies from the USA have revealed that the prevalence of HSV-2 infections in adults increased from 16.4% in 1976–1980³ to ~22% in 1988–1994.⁴ In addition, studies in pregnant women in Seattle, USA, revealed a seroprevalence of 32%.⁵ Unfortunately no national HSV-2 seroprevalence studies have been undertaken in Australia; much of the prevalence data have been derived from small studies in highly selective

populations. In these studies, the reported HSV-2 prevalence was 15–70% in sexually transmitted infection (STI) clinic attendees,^{6,7} 20% in HIV antibody-negative and 61% in HIV antibody-positive males,⁸ 58% in female prisoners and 21% in male prisoners.⁹ In contrast, studies from antenatal clinics have shown that HSV-2 antibodies are detected in only 12–15% of pregnant women.^{7,10} The latter studies were conducted at the same hospital almost a decade apart (late 1980s and 1995–1998) and suggest that local HSV-2 prevalence rates remained virtually identical over this period. The risk factors for HSV-2 infection in this antenatal population included sexual and social factors that were similar to those found in studies in other countries, such as: increasing age; poorer educational attainment; absence of private health insurance; Asian ethnic origin; earlier age at coitarche; more than one sexual partner; sexual partner with genital HSV infection; and previous chlamydia infection.¹¹ Overall these data suggest that while HSV-2 infection is common in high-risk populations in Australia, in pregnant women HSV-2 prevalence is considerably lower than in the USA.

The prevalence of HSV-1 in adults may have decreased in some European countries^{12,13} and the USA,¹⁴ and this difference may account for the increasing incidence of HSV-1 genital infection in some communities.^{15–20} In Australia however, HSV-1 seroprevalence in adults is ~80% and there is no evidence of a recent decrease.¹¹ This supports the view that a smaller proportion of women in Australia are at risk of acquiring both genital HSV-1 and HSV-2.

The risk of neonatal herpes acquisition appears to be highest when maternal infection occurs late in the third trimester and seroconversion has not occurred before delivery.² The incidence of primary herpes infection in pregnancy will therefore partly determine rates of neonatal herpes in a population. In a study of over 2000 women attending a large Sydney teaching hospital, the annualized HSV-2 seroconversion rate during pregnancy was 0.34%;¹⁰ considerably lower than rates from Seattle (1.89%),²¹ Helsinki (1.19%)²² and Stanford (0.58%).²³ Thus, there appears to be a reasonable correlation between HSV-2 seroprevalence and the rate of HSV-2 infection during pregnancy.¹⁰

Overall, the high HSV-1 seroprevalence, relatively low HSV-2 seroprevalence and very low HSV-2 acquisition rate in pregnancy provide reasonable explanations for the rarity of neonatal herpes in Australia. One further possible explanation relates to maternal age. The median age at first birth in Australia is 27.1 years,²⁴ following a generally upward trend, compared with 24.5 years in the USA.²⁵ This difference suggests that women in Australia are older when they

fall pregnant, possibly reducing the likelihood of partner change during pregnancy. These older women are more likely to be HSV-1 positive, if not HSV-2 positive, and therefore their risk of acquiring HSV-2 during pregnancy is reduced.^{11,26,27}

Herpes Management in Pregnancy

There is no clear consensus concerning the management of women with genital herpes in pregnancy in Australia. All pregnant women are eligible for ante-natal, delivery and post-natal care through a 'national' health system (Medicare), but approximately one-third have private healthcare insurance or pay for treatment. Obstetricians in Australia may work across public and private sector sites, resulting in considerable variation in care. Caesarean section rates in Australia are generally low, at 6.6% for planned and 6.8% for emergency sections,¹¹ but rates increase with rising maternal age, for medical or obstetric complications and for privately insured patients.

One study showed that women at risk of having an infant with neonatal herpes infection (assessed through ante-natal HSV type-specific serological screening) are more likely to have been born outside Australia and of lower socio-economic status.¹¹ They are usually attending public hospitals and are more likely to have midwife-delivered care. However, these findings were at variance with the national surveillance of neonatal herpes, where 80% of mothers with infected infants were Australian-born (the remaining 20% came from European Community countries).¹

Neither the Royal Australian College of Obstetricians and Gynaecologists (RACOG) nor the Australian College of Midwives (ACMI) produce guidelines for managing women with genital herpes in pregnancy, although RACOG has recently endorsed guidelines published by the Australasian Society for Infectious Diseases (ASID),²⁸ discussed below.

Only 34% of respondents to an Australian doctors' survey stated that their hospital had a policy for managing genital herpes in pregnancy.²⁹ For this survey, conducted to document clinical practice for managing genital herpes in pregnant women,²⁹ a questionnaire was posted to all doctors associated with RACOG; 2855 (67.3%) returned questionnaires. To assess management, clinicians were asked to consider five scenarios and judge whether caesarean sections were appropriate. These scenarios demonstrated considerable variations in practice. Most Australian obstetricians (96%) would perform caesarean sections on women with active herpes at delivery, irrespective of whether the infection was primary or recurrent. Many also recommended a caesarean section for any woman with a history of recurrent genital herpes, irrespective of the clinical scenario. Trainees appeared to be more familiar with recent developments in managing herpes infection, regarding the timing of the caesarean section and efficacy of the section in preventing transmission. They also stated that they would be less likely to perform caesarean sections at maternal request.

These findings may reflect the medico-legal implications of non-intervention in cases of recurrent genital herpes – it is often the consultant in charge rather than the trainee who has to defend a case of medical negligence. In reality, doctors' practices are often dictated by what is seen to be defensible and safe rather than by evidence-based best practice.

Recent guidelines published by ASID on the management of perinatal infections contain detailed algorithms for the management and prevention of neonatal herpes infection. These guidelines recommend caesarean sections for women who present with first-episode genital herpes in labour or in late pregnancy, where the HSV serostatus is negative or is unknown. They also recommend suppressive aciclovir therapy (400 mg orally, three times daily) during labour in these

cases.²⁸ Broad acceptance and impact of these recommendations is yet to be assessed.

Managing Neonatal HSV Infection

Diagnosing HSV infection during the neonatal period requires a high index of suspicion. As the condition is uncommon in many regions, diagnostic difficulties are not just confined to countries like Australia where the disease prevalence is low. A recent report from the USA, where the highest rates of neonatal HSV infection are reported, found that the interval between symptom onset and therapy initiation has not decreased over the last two decades, resulting in ongoing high rates of mortality and morbidity.³⁰ Data from a recently completed 6-year active surveillance in Australia suggest that the time to initiation of therapy and the overall outcome (at cessation of therapy), are comparable to those reported in the USA,¹ suggesting that a lower prevalence rate does not imply a lower rate of early diagnosis.

Factors that contribute to delays in the diagnosis of neonatal HSV disease are the absence of skin vesicles seen in up to 30% of HSV-infected infants,³⁰ including up to 70% of infants with disseminated infection or encephalitis, and the non-specific nature of the associated clinical features (i.e. fever, temperature instability, seizures, disseminated intravascular coagulation [DIC], hepatitis and pneumonitis).³¹ Furthermore, infants at high risk of developing HSV disease (such as the offspring of women with primary genital HSV infection) are hard to identify, because many are born to women with asymptomatic and/or unrecognized genital HSV infection.³² Routine ante-natal screening programmes are not cost-effective even in regions of high prevalence of genital herpes.³³ Thus, neonatal HSV infection must be considered in any infant with mucocutaneous vesicles, or the signs of sepsis with negative cultures at 48 h and/or in association with hepatitis and/or DIC, seizures or pneumonitis. There must be prompt investigation and initiation of empirical parenteral high-dose aciclovir (60 mg/kg per day divided into three doses, given intravenously).

The diagnosis of neonatal HSV infection is confirmed by isolation of HSV from a skin lesion, nose or throat swab, conjunctiva or occasionally from cerebrospinal fluid (CSF), detection of HSV DNA in the CSF, blood, or surface specimen, and/or by detection of viral antigen by direct immunofluorescence on a skin scraping from an infected cutaneous site. Diagnosis of central nervous system (CNS) HSV infection in the newborn is sometimes difficult because CSF pleocytosis is not always present and negative polymerase chain reaction results do not exclude the diagnosis. In addition, signs of encephalitis on computer tomographic imaging may be absent early in the disease course.³⁴ Supportive evidence of disseminated HSV infection includes elevated liver transaminases, thrombocytopenia or disseminated intravascular coagulopathy. Serology is unhelpful in making the diagnosis, as a significant proportion of infants never develop HSV-specific antibodies even at 12 months.

The duration of 'high-dose' parenteral aciclovir therapy for suspected cases of neonatal herpes depends on confirmation of the diagnosis and the category of disease. Current recommendations in Australia²⁸ are in accord with international guidelines and specify that infants with disease localized to the skin, eye or mouth should be treated for 14 days, and infants with CNS disease or disseminated infection should be treated for 21 days. A repeat CSF examination should be performed at the end of therapy, to confirm that CSF indices are normal and there is not persistence of HSV DNA. The impact of prolonged therapy on long-term neurological outcome under these circumstances has yet to be determined.

Conclusions

Neonatal herpes is uncommon in Australia. There may be several reasons for this. These include older age at pregnancy than in other developed countries, low HSV-2 seroprevalence in the general community, low risk of HSV-2 acquisition during pregnancy and a relatively high HSV-1 seroprevalence in adults in Australia. While the recently published ASID recommendations for herpes management in pregnancy have been endorsed by RACOG, neither they, nor ACMI, have produced their own guidelines for the management of herpes in pregnancy.

Finally, the diagnosis and management of neonatal HSV infection is uniformly difficult the world over. Until an effective strategy to prevent neonatal infection and/or disease is developed, efforts in Australia (and the rest of the world) must be directed towards improving

the early diagnosis of HSV disease in the neonate and developing more effective strategies to reduce early reactivation and long-term morbidity.

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