# Antenatal screening for HSV-1 and-2 infection to prevent neonatal herpes infection

**Catherine Peckham**
**September 2006**

## 1.0 The Condition

### *1.1 Severity of the disease and size of the problem*

Neonatal herpes is a rare but potentially serious viral infection associated with high morbidity and mortality, even with antiviral therapy.

About a third of infants with neonatal herpes present with isolated lesions of the skin, eye or mouth, a third with localized CNS involvement such as encephalopathy with or without skin lesions, and a third with disseminated disease involving multiple organs. Neonatal infection is associated with a high mortality, around 20%, and about 50% of infants who survive have persisting moderate or severe neurological impairment. Neonates presenting with localized HSV infection have a better prognosis than those with disseminating or neurological disease.

The main risk of HSV transmission to the neonate is at term following exposure to infected genital secretions during vaginal delivery; perinatal infection accounts for about 85% of all cases of neonatal herpes. A further 5% of neonatal infections result from intrauterine infection and around 10% from post natal infection acquired from contact with infected individuals. Transmission of HSV to the neonate can occur following symptomatic maternal recurrences as well as episodes of asymptomatic virus shedding. However, two thirds of infected infants are born to women with no clinical evidence of disease, most of whom have no history of genital infection[1].

Neonatal infection is rare in the UK: active surveillance through the British Paediatric Surveillance Unit (BPSU) in 1986-1991 identified 76 cases, a prevalence of 1.65 per 100,000 live births (95% CI 1.3-2.0)[2]. Since then diagnostic techniques have improved and epidemiological studies suggest a continuing decline in the acquisition of HSV-1 in childhood in the UK with an increase in the number of HSV-naive adults. Repeat surveillance of neonatal herpes currently being conducted through the BPSU confirms that HSV remains rare although about 60 cases were identified in 2004-2005 and the estimated prevalence has doubled to about 4 per 100,000 live births[3]. This rate is similar to that reported in Australia (3.9 per 100,000)[4] and lower than the rate of 20-50 per 100,000 reported in the US[1].

## 1.2 The *epidemiology of the condition and its natural history*

There are two strains of herpes simplex virus; HSV-1 and HSV-2. HSV-1 is usually acquired in early life and presents as oro-labial herpes whereas HSV-2 is associated with sexual activity and is seldom present until after puberty.

In adults primary genital herpes is usually caused by HSV-2 although HSV-1 is increasing as a cause of first episode genital disease. Around half the cases of neonatal herpes reported in the UK were due to HSV-I, in contrast to the US where most cases are due to HSV-2.

The risk of a neonate acquiring neonatal herpes is influenced by the following factors:

- Infants of women shedding HSV as a result of recently acquired genital HSV infection are at higher risk of acquisition of neonatal infection than those of women with HSV reactivation**. The risk of virus transmission is greatest if a seronegative woman has a first episode of genital herpes infection near the time of delivery, prior to developing protective antibodies[5].**

- The risk of neonatal infection has been associated with long duration of rupture of the membranes[6] and the use of invasive obstetrical procedures such as fetal scalp electrodes[1, 7].

In England and Wales the incidence of HSV-1 in childhood has been falling with an increase in adult infection. The overall prevalence of HSV-2 remains low with about 5% of women showing serological evidence of infection[8]. This is lower than that described in the US where around 22% of the general population was HSV-2 seropositive[9]. However, the prevalence of HSV varies widely within subgroups of the population[10]. Previous oro-labial infection with HSV-1 in childhood provides protection against genital HSV-1, and a decline in the prevalence of HSV-1 in childhood therefore increases the pool of adults at risk of a primary HSV-1 genital infection. Although previous HSV-1 offers little protection from acquiring HSV-2 it may modify the severe clinical manifestations of a primary genital HSV-2 infection.

Natural history studies indicate that women who have first episode disease are more likely to have cervical infection and to shed larger quantities of virus for a longer period than women with a recurrence of genital herpes.

After a primary infection the virus remains latent and the infected person experiences recurrent viral reactivations that can be symptomatic or asymptomatic.

The best evidence regarding the natural history of pregnancies at risk for neonatal herpes transmission was provided by a prospective study of 7046 pregnant women who were seronegative for HSV-1 and HSV-2 and were followed for seroconversion in pregnancy[11]. There were 94 (2%) seroconversions before term and no cases of neonatal herpes. There were however nine infants born to women who acquired HSV infection at the time of delivery, prior to developing HSV antibodies. Four of these infants developed neonatal herpes: two were HSV-1 infected. This study illustrates the low risk of transmission once antibodies develop compared with the high transmission associated with a perinatal primary HSV infection.

## 2.0 Primary prevention of neonatal herpes

The overall prevention of sexually transmitted infections in men and women remains of key importance. Pregnant women with no history of genital herpes may reduce their risk of acquiring herpes by using condoms or abstaining from sexual intercourse during the third trimester of pregnancy. Female partners of men with genital herpes, who themselves have no history of genital herpes, should be advised about reducing the risk of acquiring this infection[12].

## 3.0 Approaches to screening for HSV in pregnancy

There are two potential strategies for screening pregnant women to avoid neonatal herpes:

### 3.1 Universal serological screening in early pregnancy

This would aim to identify women at risk of acquiring HSV infection (seronegative women) and those with prior infection with HSV. Sensitive, type-specific tests that can differentiate between HSV-1 and HSV-2 are now commercially available and can determine a woman's susceptibility to HSV infection in pregnancy.

**3.1.1** Seronegative women could be offered advice about potential ways of reducing their risk of acquisition of virus, particularly during the third trimester of pregnancy – either by using a condom during sexual intercourse or abstaining from intercourse except with sexual partners known to be free from infection. There is currently no evidence of whether or not this is likely to be an effective approach to prevention. The vast majority of women receiving this advice would be at extremely low risk and it seems doubtful whether this strategy would have any significant effect or that it would be cost effective[13].

**3.1.2** Seropositive women could be offered screening for recurrent infection as detailed below in section 3.2.

### 3.2 Virological testing of women with a history of infection and/or HSV seropositive women to detect asymptomatic virus shedding in the third trimester of pregnancy (around 35 weeks).

This approach was adopted in the US in the 1990s when it was recommended that all women with a history of genital herpes should have weekly viral cultures taken from 34 weeks gestation so that those with a positive culture could be delivered by caesarean section. This approach would exclude women with premature delivery and those who booked late in pregnancy, groups at increased risk of infection.

There is no clear evidence that this intervention reduces the risk of neonatal infection and this approach is no longer recommended. The risk of transmission is low in this group and antenatal swabbing does not accurately predict shedding of virus at the onset of labour[14]. Asymptomatic women identified with a positive culture in late pregnancy could potentially be offered antiviral therapy to reduce virus shedding but the evidence for the effectiveness of currently available antivirals is limited. Elective Caesarean section performed before onset of labour, or within a short time after the rupture of membranes, is likely to reduce the risk of transmission although the magnitude of the effect has not been clearly quantified. There are however important although uncommon adverse consequences associated with Caesarean section which would have to be weighed against the relatively low risk of transmission in women with asymptomatic viral shedding after recurrence during pregnancy.

Primary genital herpes infection in late pregnancy is a situation where the risk of Caesarean section is probably outweighed by the potentially devastating consequences of neonatal herpes infection which is a much higher risk in these circumstances. Most experts would counsel delivery by Caesarean section in these circumstances, notwithstanding the paucity of high quality evidence of effectiveness in reducing transmission.

## 4.0 The Tests

Serological tests for HSV-2 are relatively accurate but, as with all tests false positive and false negative results can occur. Given the relatively low prevalence of past infection in women in the UK, it is likely that many women who screen positive will in fact be false positives. The consequences of such false positive tests, even if they are subsequently found to be incorrect, can be considerable. To avoid this scenario it would probably be necessary to confirm all positive tests, raising the overall programme costs.

The same general points apply to viral cultures with the inevitable problems associated with both false positives and false negatives.

# Conclusion

**Universal serological screening should not be offered to pregnant women as there is no evidence that screening pregnancies to identify women at risk of new infections will effectively decrease the incidence of infections in the perinatal period.**

**Screening of seropositive women or those with a history of genital infection in the third trimester of pregnancy (eg at 35 weeks) to identify those with asymptomatic shedding of virus near delivery has little value. The risk of neonatal infection in infants born to this group is low and the evidence that either drug treatment or the performance of elective Caesarean section in this group of women reduces transmission is limited. Most neonatal infections occur as a result of a first episode maternal HSV infection during late pregnancy before the development of protective maternal antibodies.**

**Efforts need to be focused on improving the early diagnosis and treatment of neonatal HSV disease and on ensuring appropriate action where primary maternal infection occurs during late pregnancy.**

September 2006


1.Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serological status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant, JAMA,2003;289:202-9.

2. Tookey P, Peckham CS. Neonatal herpes simplex virus infection in the British Isles. Paediatr Perinat Epidemiol 1996:10;432-42.

3. Unpublished data 2006.

4. Australian Paediatric Surveillance Unit 2002.

5. Prober CG, Sullender WM, Yasukawa LL. Au DS, Yeager AS, Arvin AM. Low risk of herpes simplex virus infections in neonates exposed to the virus at the time of vaginal delivery to mothers with recurrent herpes simplex virus infections. N Engl J Med1987; 316:240-4.

6. Nahmias AJ, Josey WE, Naib ZM, Freeman MG, Fernandez RJ, Wheeler JH. Perinatal risk associated with maternal genital herpes simplex virus infection. Am J Obstet Gynecol 1971; 110:825-37.

7. Amann ST, Fragnant RJ,Chartrand SA,Monif GR. Herpes simplex infection associated with short term use of a ftal scalp electrode. A case report. J Reprod Med 1992; 37:272-4.

8.Vyse AJ, Gay NJ, Slomka MJ, Gopal R, Gibbs T, Morgan-Capner P, Brown DW. Sex Transm Inf 2000; 76:183-87.9. Flemming DT, Quillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* 1997;337:1158-9.

10, Ades AE, Peckham CS, Dale GE, Best J. Prevalence to antibodies to herpes simplex virus types I and 2 in pregnant women and estimated rates of infectionJ Epidemiol Commun Health1989;43:53-60.
11. Brown ZA, Selke S, Zeh J, Kopelman J, Maslow A, Ashley RL, et al. The acquisition of herpes simplex virus during pregnancy. N Engl J Med 1997; 337:509-15.
12. Management of Genital Herpes in Pregnancy. RCOG guideline No.30; 2006.
13. Qutub M, Clapper P, Vallely P, Cleator G. Genital herpes in pregnancy: is screening cost effective? International Journal of STD and AIDS 2001; 12:14-16.
14. Arvin AM, Hensleigh PA, Prober CG,Au DS, Yasukawa LL, Wittek AE et al Failure of antepartum maternal cultures to predict the infants risk of exposure to herpes simplex virus at delivery. N Engl J Med 1986; 315:796-800.