



CHAPTER

10

*Prevention  
of Neonatal  
Herpes Simplex*

By Elaine E. L. Wang

# Prevention of Neonatal Herpes Simplex

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*Herpes simplex infection in the newborn is thought to be acquired from the mother during passage through an infected birth canal. Experts agree that the infant's exposure to the virus can be prevented by cesarean section if the maternal infection is recognized at the onset of labour and within 4 to 6 hours after rupture of the membranes. However, maternal infection is asymptomatic in 70% of cases. The difficulty in detecting asymptomatic infection has led to the practice of screening women considered to be at high risk (those with a history of recurrent genital infection or active disease during the current pregnancy and those whose sexual partners have proven genital herpes).*

*However, identification and screening of pregnant women at risk of recurrent infection has not been shown to prevent neonatal death or illness from infection and is not recommended. There is currently no screening strategy for asymptomatic women with no known history of herpes virus exposure, even though the risk of transmission to the newborn is higher in primary infections.*

## Burden of Suffering

The clinical presentation in 70% of cases of neonatal herpes simplex is skin involvement consisting of cutaneous vesicles. If the cutaneous infection is not treated systemic infection will develop within a week in two-thirds of the infants. The clinical presentation in 20% of cases is major systemic involvement, central nervous system involvement, or both. Less than 10% of babies with neurologic disease develop normally. The overall mortality rate among infants with untreated infection is 65%.

The rising incidence of neonatal herpes simplex has reflected a nationwide increase in the prevalence of herpes simplex. In 1981 the incidence was 12 cases per 100,000 live births, as estimated from a hospital-based study in Washington. In other studies primary infection was responsible for 29-35% of cases. Although both the transmission rate and the attack rate are higher with primary infection, recurrent infection accounts for a greater proportion of the burden of neonatal infection.

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## Maneuver

The target group of women with recurrent infection may be identified through history-taking or detection of herpes simplex virus antibodies by microneutralization. The latter is expensive and unavailable for routine use. Since more than 50% of pregnant women with herpes simplex deliver prematurely, usually between 30 and 37 weeks' gestation, weekly screening is started in the 32nd week of gestation. Women whose most recent culture results or findings at clinical examination were positive for herpes virus undergo cesarean section. Women whose last culture results and findings at clinical examination were negative have vaginal delivery. The decision to do weekly screening depends on the mother's ability to recall previous episodes. Patient recall, however, is not reliable. In one study involving 11 women claiming to be having their first episode of herpes simplex, 5 women had antibodies indicating previous infection. In seroepidemiologic studies of herpes simplex type 2 infection, only 33% of the seropositive patients were aware of previous infection. In another study only 1 of 12 seropositive women indicated a history of disease or of contact with an infected person. A U.S. Centers for Disease Control surveillance study involving 184 cases showed that only 22% of mothers had a history of genital herpes simplex virus (HSV) infection and only 9% had genital lesions at the time of delivery.

The screening test consists of culture of a cervical smear for herpes simplex virus. However, since the results are not available for 3 days, the decision to deliver vaginally or by cesarean section is usually based on the penultimate culture result, which has a very low predictive validity for the presence of infection at the time of delivery. Arvin and associates<sup>1</sup> followed 414 women with a history of recurrent genital herpes. None of 17 women with positive antepartum culture results had positive results at delivery, and 5 of 354 asymptomatic mothers with negative antepartum results had positive results at delivery (sensitivity 0%).



Antepartum cultures have poor sensitivity and specificity for demonstrating viral shedding at delivery

## Effectiveness of Prevention and Treatment

### Weekly Screening

Since the policy of weekly screening addresses only the problem of recurrent infection, asymptomatic women with primary infection do not benefit at all, yet their infection lasts longer and is more likely to be associated with greater amounts of virus shedding.<sup>2,3</sup> The risk of transmission to the newborn has been estimated to be 50% in cases of primary infection and the probability of clinical disease in the infant (attack rate) 17% to 20%.



Primary maternal infection is associated with a higher transmission rate and more severe neonatal disease than is recurrent infection

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Not only is the risk of transmission higher in primary infection, but the outcome is more likely to be severe. Prober and collaborators<sup>4</sup> studied the hypothesis that serologically verified primary infection would be associated with a worse neonatal outcome than that associated with recurrent infection. Through screening of 6,904 mother-infant pairs for both herpes simplex virus antibodies and herpes simplex at delivery they identified infection in 14 women and 3 infants. Two of the three infants were born of the two mothers with primary infection; meningitis developed in one of the two infants at 12 days of age.

Among women with recurrent disease the risk of transmission and clinical disease in the newborn appears to be lower. Of 34 infants inadvertently delivered vaginally from mothers with recurrent infection at the time of delivery and followed up without treatment, all remained asymptomatic. Calculation of the 95% confidence interval within which the mean risk of disease could be expected among these infants resulted in an upper estimate of risk of 8%. A genital lesion consistent with herpes simplex was present in 56% of the mothers, underscoring the importance of careful clinical examination among asymptomatic women.

Decision analysis was used to evaluate 9 strategies for prevention of neonatal HSV (involving physical exam, culture, and antigen testing of all or high-risk women). Physical examination at labour was found to be the optimal strategy given the goal of minimizing the ratio of excess cesarean sections to cases of neonatal HSV infection averted; however, about 30 excess cesarean sections would be performed for each case averted. Strategies involving high-risk women were associated with 36-178 excess cesarean sections per HSV case averted.

The use of cesarean section among symptomatic women only will lead to some missed cases; however, an economic evaluation of the strategy of sequential screening revealed that it would cost US\$37 million for each case prevented. A national screening program in the U.S. would prevent 1.8 cases/year.

## Recommendations of Others

Because of the limitations of screening only those at high risk, the Committee on Infectious Disease of the American Academy of Pediatrics no longer supports screening.<sup>5</sup>

The Infectious Diseases and Immunization Committee of the Canadian Pediatric Society recommends that all pregnant women be questioned during prenatal visits about any personal history of genital HSV infection or similar history in their sexual partner(s). Signs and symptoms of genital HSV infection should be sought in all women during pregnancy but weekly antepartum cultures for HSV are not recommended, even in women with a history of genital HSV infection.

However, all women should be questioned about recent symptoms and examined carefully for clinical evidence of genital HSV infection on admission for delivery; and all newborn infants whose mothers have genital lesions or a history of infection should be examined/observed.

The U.S. Preventive Services Task Force recommends screening pregnant women with active lesions for genital herpes simplex virus; this recommendation is currently being reviewed.

In December, 1992, the Infectious Disease Society of America (IDSA) recommended that serial viral cultures for women with recurrent infections be abandoned. The IDSA recommended that women with histories of genital herpes should be provided education and reassurance. Assays for detection of HSV antigen or viral cultures should not be performed except to evaluate clinically apparent lesions. While routine samples for cultures were recommended at delivery for women with histories of genital herpes, even in the absence of visible lesions, the lack of established utility for such screening was emphasized. If the patient had active genital herpes when labour occurred (not including active lesions at some distance from the genital tract, e.g. buttock), cesarean section was recommended before membrane rupture or as soon thereafter as possible and viral cultures performed.

## Conclusions and Recommendations

Weekly screening among women at high risk for herpes simplex cannot be recommended because 1) it does not address prevention among asymptomatic women with primary infection; 2) history-taking does not adequately identify women at risk of recurrent infection; 3) the predictive validity of the penultimate culture is very poor; 4) the attack rate of recurrent infection is low; and 5) the preventive intervention, cesarean section, is associated with increased maternal morbidity and mortality rates and costs, as compared with vaginal delivery.

A high degree of suspicion of herpes simplex must be maintained since neonatal herpes simplex is usually severe by the time of presentation. Empiric initiation of antiviral therapy should be considered.

Based on fair evidence from well-designed cohort studies, weekly culture for herpes simplex virus should be excluded from the routine prenatal care of women with a history of recurrent herpes simplex (D Recommendation).

A history of genital herpes and clinical evidence of infection at the time of delivery should be sought. If such evidence exists, cesarean section is recommended, particularly if it is known before or within 4 to 6 hours after rupture of the membranes. However, this strategy is based upon expert opinion; there is overall poor evidence



For women with clinical herpes simplex perineal infections, perform cesarean section if membranes have ruptured within 4-6 hours

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to include cesarean section in, or exclude it from, routine prepartum care of symptomatic women (C Recommendation).

## Unanswered Questions (Research Agenda)

The following have been identified as research priorities:

1. Determining whether cesarean section does more good than harm among women with symptomatic herpes simplex. Evaluating new serologic methods for identifying women at risk for primary infection – that is, seronegative women who are at greater risk of transmitting disease to their infants – in order to allow targeting of investigations in that group.
2. Developing rapid diagnostic tests with adequate sensitivity and specificity for use among asymptomatic women so that interventions can be performed in time to prevent neonatal infection.
3. Evaluating the use of new antiviral agents among pregnant women for the prevention of neonatal herpes simplex.

## Evidence

The literature was identified with a MEDLINE search to March, 1993, using the following MESH headings: herpes simplex, pregnancy, and infant, newborn.

This review was initiated in October 1988 and recommendations were finalized by the Task Force in February, 1989. A report with a full reference list was published in December 1989.<8>

## Selected References

1. Arvin AM, Hensleigh PA, Prober CG *et al*: Failure of antepartum maternal cultures to predict the infant's risk of exposure to herpes simplex virus at delivery. *N Engl J Med* 1986; 315: 796-800
2. Corey L, Spear PG: Infections with herpes simplex virus (1). *N Engl J Med* 1986; 314: 686-691
3. Corey L, Spear PG: Infections with herpes simplex virus (2). *N Engl J Med* 1986; 314: 686-691
4. Prober CG, Hensleigh PA, Boucher FD, *et al*: Use of routine viral cultures at delivery to identify neonates exposed to herpes simplex virus. *N Engl J Med* 1988; 318: 887-891
5. Committee on Infectious Diseases: *1988 Red Book*, 21st ed, American Academy of Pediatrics, Elk Grove Village, Ill, 1988: 230-239

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6. U.S. Preventive Services Task Force: *Guide to Clinical Preventive Services: an Assessment of the Effectiveness of 169 Interventions*, Williams & Wilkins, Baltimore, Md, 1989: 151-154
  7. Prober CG, Corey L, Brown ZA, *et al*: The management of pregnancies complicated by genital infections with herpes simplex virus. *Clin Infect Dis* 1992; 15: 1031-1038
  8. Canadian Task Force on the Periodic Health Examination: The periodic health examination, 1989 update part 4, Intrapartum electronic fetal monitoring and prevention of neonatal herpes simplex. *Can Med Assoc J* 1989; 141: 1233-1240



## Prevention of Neonatal Herpes Simplex

MANEUVER	EFFECTIVENESS	LEVEL OF EVIDENCE <REF>	RECOMMENDATION
<b>Recurrent infection</b> Weekly screening (starting at 32 weeks' gestation); cesarean section among women with positive culture results or findings at clinical examination	Identification and screening of pregnant women at risk of recurrent infection has not been shown to prevent neonatal death and illness from infection.	Screening trial and prospective cohort study<1-4> (II-2)	Fair evidence to exclude from routine prepartum care in high-risk pregnancies* (D)
<b>Symptomatic infection</b> Clinical examination; cesarean section among women with positive findings at clinical examination	Transmission of herpes simplex to newborn can be prevented among women with clinical evidence of genital herpes simplex at delivery.	Expert opinion<5,7> (III)	Poor evidence to include cesarean section in or exclude it from routine prepartum care of symptomatic women (C)

\* Women at high risk are those with a history of recurrent herpes simplex or active disease during current pregnancy and those whose sexual partner has proven genital herpes simplex.