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Effect of Serologic Status and Cesarean Delivery on Transmission Rates of Herpes Simplex Virus From Mother to Infant

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THE PREVALENCE OF GENITAL and neonatal herpes in the United States continues to rise.¹ About 1.6 million new herpes simplex virus (HSV) 2 infections are acquired yearly and more than 2% of women seroconvert to HSV-2 during pregnancy.^{2,3} Although previous studies suggest that neonatal HSV infection is often a consequence of HSV acquisition in late pregnancy,³⁻¹⁰ the risk of transmission of HSV-1 or HSV-2 from mother to infant as it relates to maternal HSV serologic status and exposure to HSV in the maternal genital tract at the time of labor has not been quantified. Furthermore, cesarean delivery has been the standard of care for more than 3 decades for women with genital herpes lesions at the time of delivery, but no data exist on whether this procedure reduces HSV transmission, and some obstetrical authorities have discussed abandoning this practice.¹¹⁻¹⁶

To evaluate the risk factors for the transmission of HSV from mother to infant, women in labor had a genital viral culture obtained and serum samples saved for retrospective analysis of HSV-1 and HSV-2 serologic status.

Context Neonatal herpes most commonly results from fetal exposure to infected maternal genital secretions at the time of delivery. The risk of transmission from mother to infant as it relates to maternal herpes simplex virus (HSV) serologic status and exposure to HSV in the maternal genital tract at the time of labor has not been quantified. Furthermore, no data exist on whether cesarean delivery, the standard of care for women with genital herpes lesions at the time of delivery, reduces HSV transmission.

Objective To determine the effects of viral shedding, maternal HSV serologic status, and delivery route on the risk of transmission of HSV from mother to infant.

Design Prospective cohort of pregnant women enrolled between January 1982 and December 1999.

Settings A university medical center, a US Army medical center, and 5 community hospitals in Washington State.

Patients A total of 58362 pregnant women, of whom 40023 had HSV cultures obtained from the cervix and external genitalia and 31663 had serum samples tested for HSV.

Main Outcome Measure Rates of neonatal HSV infection.

Results Among the 202 women from whom HSV was isolated at the time of labor, 10 (5%) had neonates with HSV infection (odds ratio [OR], 346; 95% confidence interval [CI], 125-956 for neonatal herpes when HSV was isolated vs not isolated). Cesarean delivery significantly reduced the HSV transmission rate among women from whom HSV was isolated (1 [1.2%] of 85 cesarean vs 9 [7.7%] of 117 vaginal; OR, 0.14; 95% CI, 0.02-1.08; $P=.047$). Other risk factors for neonatal HSV included first-episode infection (OR, 33.1; 95% CI, 6.5-168), HSV isolation from the cervix (OR, 32.6; 95% CI, 4.1-260), HSV-1 vs HSV-2 isolation at the time of labor (OR, 16.5; 95% CI, 4.1-65), invasive monitoring (OR, 6.8; 95% CI, 1.4-32), delivery before 38 weeks (OR, 4.4; 95% CI, 1.2-16), and maternal age less than 21 years (OR, 4.1; 95% CI, 1.1-15). Neonatal HSV infection rates per 100000 live births were 54 (95% CI, 19.8-118) among HSV-seronegative women, 26 (95% CI, 9.3-56) among women who were HSV-1-seropositive only, and 22 (95% CI, 4.4-64) among all HSV-2-seropositive women.

Conclusion Neonatal HSV infection rates can be reduced by preventing maternal acquisition of genital HSV-1 and HSV-2 infection near term. It can also be reduced by cesarean delivery and limiting the use of invasive monitors among women shedding HSV at the time of labor.

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METHODS Participants, Setting, and Procedures

This study was carried out at University of Washington Medical Center, Se-

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attle, between January 1982 and December 1999, at 5 community hospitals in Seattle between January 1984 and October 1990, and at Madigan Army Medical Center, Tacoma, Wash, between August 1990 and September 1997. Viral cultures were obtained from women in labor by swabbing the vulva, perineal, and perianal areas. A separate swab was used to obtain a sample from the upper vagina and cervix.^{3,8} If genital lesions were identified on examination during delivery and the peripartum period, cultures were obtained from the lesion and placed in a separate vial of transport media.¹⁷ Only women who had cultures obtained within 48 hours of delivery were included in the analysis. Prophylactic acyclovir therapy was not used during pregnancy, at delivery, or during the immediate postpartum period for any of the exposed infants.^{11,12,18} Maternal HSV serologic status was determined from samples collected at delivery or at obstetrical antepartum testing. Culture results were reported to the attending physician, as were the results of HSV serologic tests after the test became available for clinical use. Written informed consent was obtained for the portions of the study protocol not included in routine clinical care according to the University of Washington Institutional Review Board.

Data Collection

Routine demographic and delivery data were collected on deliveries at all hospitals from 1989-1999 and at the University of Washington during the entire 18-year study period. Delivery room charts were reviewed for history and signs of genital herpes, duration of membrane rupture, and route of delivery in women from whom HSV was isolated at delivery and in women whose infants developed neonatal herpes.

Laboratory Methods

Herpes simplex virus cultures and HSV DNA detection by polymerase chain reaction were performed as previously described.^{19,20} Serum samples obtained at the time of labor were stored and tested

for antibodies to HSV-1 and HSV-2 by Western blot assay following delivery.²¹

Definitions and Statistical Analysis

The serologic and virologic classification of HSV status at delivery was defined as previously published.^{3,8,22} Women with primary-episode genital herpes were defined as having HSV-1 or HSV-2 isolated from genital secretions without having concurrent HSV antibodies. A nonprimary first-episode infection was defined as HSV-2 isolated from genital secretions of a woman with only HSV-1 antibodies, or HSV-1 isolated from a woman with only HSV-2 antibodies. Reactivation HSV-1 or HSV-2 was present when the virus isolated from genital secretions was the same type as antibodies present in the serum at the time of labor. Symptomatic shedding was defined as the isolation of HSV when genital lesions were noted on entering the labor suite, and subclinical shedding as isolation of HSV in the absence of genital lesions.^{17,22,23}

Relative risks were assessed by computing odds ratios (ORs) with 95% confidence intervals (CIs). *P* values were obtained using 2-sided χ^2 or Fisher exact tests, with *P* < .05 considered statistically significant. Adjusted ORs were obtained from bivariate logistic regression. In examining risk factors for neonatal herpes, we adjusted for only 1 confounder at a time because of the small number of infected neonates and the correlation among the risk factors. We estimated rates of neonatal infection as a function of maternal serologic status at the 2 hospitals (University of Washington and Madigan) at which routine serologic testing for HSV was performed. These were derived with the assumption that the infants of women with known serologic status were a random sample of all infants delivered, stratified by hospital and time. Because serologic status was known for most women, the estimated denominators of the rates were very precisely determined, with coefficients of variation of 1%. Standard errors for neonatal infection rates by maternal serologic status were derived by the delta method, taking into account the

uncertainty associated with the small number of cases as well as the estimated serologies. As the SEs derived by the delta method differed from SEs based on known denominators only in the fifth significant digit, CIs were based on exact CIs for binomial proportions. Statistical analyses were carried out using SPSS, version 8.0 (SPSS Inc, Chicago, Ill), and S-PLUS, version 3.1 (Insightful Corp, Seattle, Wash). The same study team carried out the study, including data management and analysis, for the entire period.

RESULTS

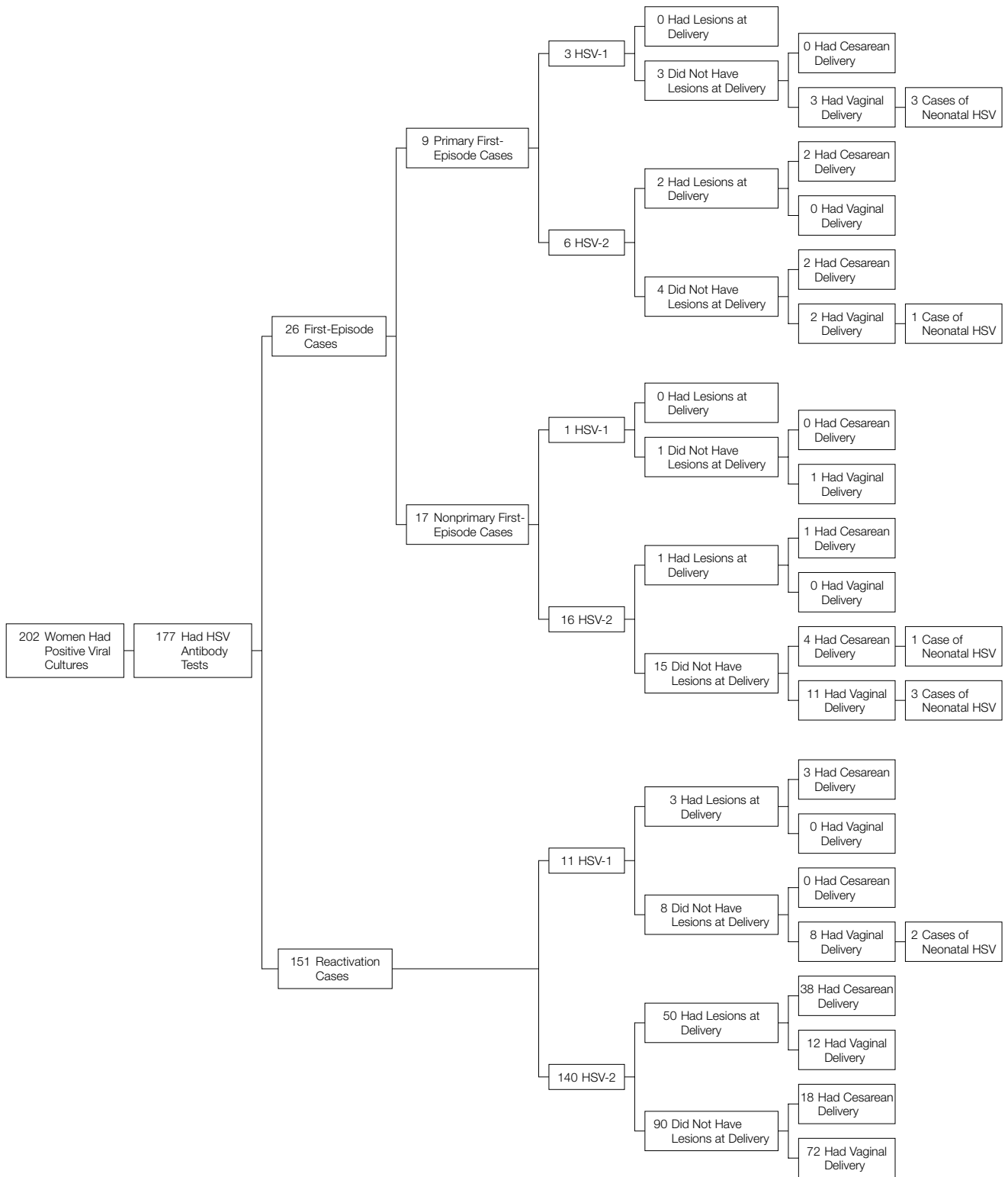
During the study period there were 58 362 live births in the study hospitals; 18 cases of neonatal HSV were identified among these live births, for a rate of 1 case of neonatal herpes per 3200 live births. Among the 18 cases, 8 neonates acquired HSV-1 and 10 acquired HSV-2 infection. Of the 10 infants with neonatal HSV-2 infection, 7 were born to mothers with primary or nonprimary first-episode HSV-2 and 3 to mothers with reactivation HSV-2 infection. Of the 8 infants with neonatal HSV-1 infection, 4 were born to mothers with primary HSV-1 and 4 to mothers with reactivation HSV-1.

Herpes simplex virus cultures were obtained within 48 hours of delivery in 40 023 (69%) of the 58 362 women. Herpes simplex virus was isolated from 202 women (0.5%). Serum samples for HSV antibody status were obtained from 31 663, including 177 (88%) of the 202 women with positive cultures (FIGURE). Of these 177 women, 26 had a first-episode genital HSV infection at delivery (3 with primary HSV-1, 6 with primary HSV-2, 1 with nonprimary HSV-1, and 16 with nonprimary HSV-2) and 151 women had reactivation of previously acquired genital HSV (11 with HSV-1, 140 with HSV-2).

Risk Factors for Transmission of Neonatal HSV

Isolation of HSV at delivery from mothers was a major risk factor for neonatal herpes (OR, 346; 95% CI, 125-956; TABLE 1). Neonatal transmission oc-

Figure. Frequency of Neonatal Herpes Simplex Virus (HSV) Among 177 Women Shedding HSV at Delivery



curred in 10 (5%) of the 202 women from whom HSV was isolated. All 3 women shedding HSV-1 due to a primary HSV-1 infection infected their infants, as did 1 (17%) of 6 women with primary HSV-2 infection, 4 (25%) of 16 women with nonprimary first-episode HSV-2 infection, and 2 (18%) of 11

women with reactivation HSV-1 (Figure). None of the 140 women with viral shedding due to reactivation HSV-2 infected their infants.

We analyzed the effect of delivery route and presence of genital lesions at delivery on neonatal transmission. Of the 202 women who had HSV isolated from genital secretions, 117 (58%) were delivered vaginally and 85 (42%) underwent cesarean delivery (TABLE 2). Lesions presumed to be caused by genital herpes were the indication for cesarean delivery in 60 (71%) of the cesarean deliveries vs 9 (7.7%) of 117 vaginal deliveries (OR, 0.14; 95% CI, 0.02-1.08; $P = .047$; Table 1). One woman with subclinical nonprimary first-episode HSV-2 infection transmitted HSV-2 to her infant after undergoing a cesarean delivery because of failure to progress 19 hours after rupture of membranes. The protective effect of cesarean delivery appeared to be similar after adjustment for stage of infection (OR, 0.14; 95% CI, 0.02-1.26) or for HSV type (OR, 0.17; 95% CI, 0.02-1.46), although no longer statistically significant.

Genital lesions at delivery were also associated with decreased risk of neonatal herpes among women with HSV isolation. Sixty women had genital lesions and underwent cesarean delivery; an additional 14 women had evidence of genital lesions on retrospective review of the case record. These women were delivered vaginally because their genital lesions were not noted until it was too late to proceed with a cesarean delivery, or immediately following delivery. None of these 74 women infected their infants in comparison with 10 of 128 women who were shedding virus without lesions ($P = .01$; Table 1 and Table 2).

Among 202 women who shed HSV at delivery, 102 had a history of genital herpes and 100 did not. Of the 10 infected infants, 4 were born to mothers with a history and the other 6 to women without a history of genital herpes. Women without a history of genital herpes were more likely to shed HSV subclinically than women with such a

Table 1. Risk Factors for Development of Neonatal HSV in a Cohort of 40 023 Women With Genital Cultures for HSV Obtained at Delivery

Risk Factors	No./Total (%) of Infants With Neonatal HSV Infection	OR (95% CI)*	P Value†	Adjusted OR (95% CI)‡
Among 40 023 Deliveries With Cultures				
HSV isolated at delivery				
Yes	10/202 (4.95)	346 (125-956)	<.001	...
No	6/39 821 (0.02)			
Among 202 Deliveries With HSV Isolated				
Type of delivery				
Cesarean	1/85 (1.2)	0.14 (0.02-1.08)	.047	0.14 (0.02-1.26)
Vaginal	9/117 (7.7)			
Lesions at delivery				
Yes	0/74 (0.0)	0	.01	...
No	10/128 (7.8)			
Invasive monitors				
Yes	8/79 (10.1)	6.8 (1.4-32)	.02	3.5 (0.6-19)
No	2/123 (1.6)			
Type isolated				
HSV-1	5/16 (31.3)	16.5 (4.1-65)	<.001	34.8 (3.6-335)
HSV-2	5/186 (2.7)			
First episode				
Yes	8/26 (30.8)	33.1 (6.5-168)	<.001	59.3 (6.7-525)
No	2/151 (1.3)			
HSV isolated from cervix§				
Yes	9/49 (18.4)	32.6 (4.1-260)	<.001	15.4 (1.8-133)
No	1/146 (0.7)			
Premature delivery (<38 wk)				
Yes	6/55 (10.9)	4.4 (1.2-16)	.03	1.7 (0.4-7.6)
No	4/147 (2.7)			
Maternal age, y				
<21	6/56 (10.7)	4.1 (1.1-15)	.03	2.7 (0.6-12)
≥21	4/142 (2.8)			

Abbreviations: CI, confidence interval; HSV, herpes simplex virus; OR, odds ratio.

*ORs and CIs were calculated by logistic regression, except where OR = 0. Where OR = 0, there were no infected infants in 1 of the comparison groups, so logistic regression could not be used.

†P values were calculated from the Fisher exact test.

‡Adjusted ORs were calculated by bivariate logistic regression. The adjusted OR for first episode vs reactivation HSV in the mother is adjusted for viral type isolated. All other adjusted ORs are adjusted for first-episode vs reactivation HSV. Ellipses indicate that adjusted ORs could not be computed.

§HSV isolated from cervix only or cervix and vulva vs HSV isolated from vulva alone.

Table 2. Delivery Route and Acquisition of Neonatal Herpes in Women With Herpes Simplex Virus Isolated From the Genital Tract, Stratified by Presence of Lesions

	Neonatal Infection	No Neonatal Infection	Total
Women with lesions present at delivery			
Cesarean	0	60	60
Vaginal*	0	14	14
Women with subclinical viral shedding			
Cesarean	1	24	25
Vaginal	9	94	103
Overall			
Cesarean	1	84	85
Vaginal	9	108	117
Total	10	192	202

*Lesions noted immediately postpartum or too late for cesarean delivery.

history (87 vs 41; $P < .001$). However, women with a history of genital herpes were more likely to have cesarean deliveries (OR, 5.7; 95% CI, 3.1-11), although this risk was attenuated by adjustment for lesions at delivery (adjusted OR, 2.3; 95% CI, 1.1-4.9).

Among women from whom HSV was isolated, the lack of maternal antibodies to the viral type shed was associated with a marked increase in the risk of transmission to the infant (OR, 33.1; 95% CI, 6.5-168; $P < .001$; Table 1). The increased transmission risk of newly acquired compared with reactivation disease remained statistically significant after adjustment for viral type (OR, 59.3; 95% CI, 6.7-525) and was true both for HSV-2 ($P < .001$) and HSV-1 infection ($P = .08$). In contrast with the protection offered by homologous antibody, heterologous antibody did not protect against HSV transmission (OR, 2.6; 95% CI, 0.5-15) for primary vs nonprimary first-episode infection.

The rate of transmission of HSV from mother to infant was higher when HSV-1 was isolated at delivery (5 [31.3%] of 16) compared with HSV-2 (5 [2.7%] of 186) (OR, 16.5; 95% CI, 4.1-65), and the risk remained significantly elevated after adjustment for newly acquired infection (OR, 34.8; 95% CI, 3.6-335). The risk of transmission was also elevated when HSV was isolated from the cervix vs from the vulva only (OR, 32.6; 95% CI, 4.1-260) and remained statistically significant after adjustment for newly acquired infection. Invasive monitoring, such as fetal scalp electrodes, was noted in 79 (39%) of the 202 women with HSV isolation at delivery and was also a significant risk factor for transmission of HSV (OR, 6.8; 95% CI, 1.4-32). Other risk factors for neonatal HSV were younger maternal age and premature delivery (Table 1), although the adjusted OR for these suggested confounding with newly acquired infection.

Women From Whom HSV Was Not Isolated at Delivery

Cultures were not obtained from 2 of the 18 women who transmitted HSV

Table 3. Transmission Rates of Neonatal HSV by Maternal HSV Serologic Status Among Women Who Delivered at the University of Washington and Madigan Army Hospitals

Maternal HSV Serostatus	No./Total (%) of Infants With Neonatal HSV	Rate per 100 000 Live Births (95% Confidence Interval)
HSV seronegative	6/11 115 (0.054)	54 (19.8-118)
HSV-1 seropositive only	6/23 480 (0.026)	26 (9.3-56)
All HSV-2 seropositive	3/13 795 (0.022)	22 (4.4-64)
HSV-2 only	2/5761 (0.035)	35 (4.2-126)
HSV-1 and HSV-2	1/8034 (0.012)	12 (0.3-70)

Abbreviation: HSV, herpes simplex virus.

and negative viral cultures were reported in 6. The viral isolates from the infants and the maternal serum samples were available in all 8 cases. One woman had primary HSV-1, 1 had primary HSV-2, 1 had nonprimary HSV-2, 2 had reactivation HSV-1, and 3 had reactivation HSV-2. We were able to retrieve the specimen obtained for viral isolation at delivery for 2 of the 6 negative cultures. Herpes simplex virus 2 DNA was detected in both.

Risk of Neonatal HSV Infection by Maternal HSV Serologic Status

To evaluate the relationship between maternal HSV serologic status and transmission, we limited our analyses to the 48390 deliveries at the 2 hospitals where HSV serologic testing was routinely performed. Fifteen of the 18 cases of neonatal herpes were from these hospitals. Among the 31 645 serum samples corresponding to these deliveries, 23% of women were HSV seronegative, 49% had only HSV-1 antibodies, 11% had only HSV-2 antibodies, and 17% had both HSV-1 and HSV-2 antibodies. TABLE 3 shows the estimated rates of neonatal HSV infection computed from these data. The highest (1 in 1900) occurred among women who had no HSV antibodies, whereas the lowest (1 in 8000) was among women who were seropositive for HSV-1 and HSV-2. The small number of observed cases limits the power to detect statistically significant differences among the rates.

COMMENT

Several novel observations about neonatal HSV infection emerged from our analyses. First, while women with all

HSV serologic classifications are at risk of transmitting HSV to their infants, the highest risk for transmitting infection to the infant was among HSV seronegative women. This high rate reflects the high efficiency of HSV transmission from seronegative women who acquire primary HSV-1 and HSV-2 and whose infants lack type-specific transplacental antibodies. Second, women with previous HSV-2 infection are at a reduced risk for transmitting HSV-2 to their infants and at essentially no risk of transmitting HSV-1. This reflects the relatively inefficient transmission of HSV-2 in the face of type-specific transplacental antibodies and the seemingly protective effect of genital HSV-2 infection on the acquisition of genital HSV-1 infection. Third, the transmission rate of HSV is highly influenced by management of women in labor, including recognition of lesions, protection offered by cesarean delivery, and maintenance of fetal skin integrity during labor.

Perhaps the most clinically important observation from our study was the finding that cesarean delivery protects against neonatal transmission of HSV. This is the first demonstration of this effect, despite that it has been standard obstetric practice in the United States for 30 years.^{5,11,12} Our data, from a cohort study that spans nearly 2 decades of management by various physicians at major service and teaching institutions, provide the first evaluation of this procedure for reducing neonatal HSV. Neonatal herpes occurred less frequently among women with genital lesions than among those experiencing subclinical shedding because women with genital lesions were more

likely to undergo cesarean delivery. Ideally, management practices such as cesarean delivery for genital herpes should be defined by randomized trials. No such trial has been undertaken in the past, and such an attempt is likely to encounter considerable ethical difficulties. Although case series of neonatal HSV show that cesarean delivery is not fully protective,^{24,25} our data indicate that it is a rational intervention and should not be abandoned.

Another novel finding was the high efficiency of transmission of HSV-1 from mother to infant, both from primary infection and reactivation of genital HSV-1, among women with genital shedding of HSV. The mechanism of this is unclear but may help explain the increasing frequency of neonatal HSV-1 infection.²⁶⁻²⁸

Development of a strategy to reduce this disease burden seems imperative. While antiviral therapy for neonatal herpes is now available, the morbidity is still high and few inroads in improving time to diagnosis have been made in the last 2 decades.^{25,29,30} As such, preventing transmission to the neonate by reducing acquisition of infection in late pregnancy in the mother and altering obstetric management may be the approach most likely to reduce neonatal HSV. Serologic assays that detect antibodies to HSV-1- and HSV-2-specific glycoprotein G1 and G2 are now commercially available³¹ and can be used to identify pregnant women who are seronegative for HSV-1, HSV-2, or both and to identify partners who present a potential risk of transmitting infection. These women can be counseled about the importance of avoiding unprotected oral-genital contact or unprotected sex in the last trimester.

Serologic screening for HSV-2 will result in identifying a large number of pregnant women with subclinical HSV-2 infections who are at risk of reactivating HSV-2 at delivery.^{17,32-35} Our data indicate that the risk of HSV transmission is low among HSV-2-seropositive women, and routine cesarean delivery is certainly not indicated. Management strategies for

HSV-2-seropositive women are complex and need systematic evaluation.³⁶⁻³⁸ Potential strategies include suppression of reactivation with antiviral therapy, examination for genital lesions and use of cesarean delivery, and identification of those shedding virus at delivery and intervention in the delivery room, such as cesarean delivery or prophylaxis of the exposed infant with antivirals. Small studies suggest that genital lesions at term may be prevented by long-term daily antiviral therapy in the last month of pregnancy, and such an approach is approved by the American College of Obstetricians and Gynecologists, but some experts still have concerns about the safety of this approach.^{11,39,40} The occurrence of false-negative cultures decreases enthusiasm for relying on viral culture alone. DNA amplification techniques offer obvious advantages and have been considered for intrapartum diagnosis of group B streptococcal infections.⁴¹ But the technological issues in conducting and reporting these assays quickly and accurately enough to influence obstetrical management are not trivial. Antiviral, behavioral, and, of course, vaccine approaches to reduce transmission from mother to infant need evaluation in large multi-institutional trials to determine the most effective and economical strategies.

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Drafting of the manuscript: Brown, Wald, Selke, Zeh, Corey.

Critical revision of the manuscript for important intellectual content: Brown, Wald, Morrow, Selke, Zeh, Corey.

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A chief event of life is the day in which we have
encountered a mind that startled us.
—Ralph Waldo Emerson (1803-1882)