OBSTETRICS

Seroprevalence of herpes simplex virus types 1 and 2 in pregnant women in the United States

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OBJECTIVE: The purpose of this study was to determine seroprevalence of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in a national cross-sectional sample of pregnant women.

STUDY DESIGN: Pregnancy tests (urine and serum) were performed for female patients 12-59 years of age who participated in the National Health and Nutrition Examination Survey from 1999-2002. Immunodot assays were used to detect antibodies to HSV-1 and HSV-2.

RESULTS: The mean age of the 626 pregnant women was 27 years, and the median number of lifetime sex partners was 4. Overall, HSV-1 seroprevalence was 63%; HSV-2 seroprevalance was 22%; infection with both HSV-1 and HSV-2 was 13%, and HSV seronegativity was 28%. HSV seroprevalence differed by race/ethnicity, with nonHispanic white patients more likely to be seronegative compared with other racial/ethnic groups (40% vs 11%; $P < .001$). The number of lifetime sex partners was also associated with serostatus. On the basis of serostatus-specific rates of neonatal herpes from a published study, the rate of neonatal herpes is projected to be 33/100,000 live births and is 40% higher in nonHispanic white women than in other racial/ethnic groups.

CONCLUSION: The seroprevalence of HSV-1 and HSV-2 varied by race/ethnicity; babies born to nonHispanic white mothers, whose HSV seroprevalence was the lowest, appear to be at greater risk for neonatal herpes.

Key words: herpes simplex virus, neonatal infection, seroprevalence, neonatal herpes

Cite this article as: Xu F, Markowitz LE, Gottlieb SL, Berman SM. Seroprevalence of herpes simplex virus types 1 and 2 in pregnant women in the United States. Am J Obstet Gynecol 2007;196:43.e1-43.e6.

Neonatal herpes is a potentially devastating infection caused by herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2).[1,2] Because neonatal herpes is acquired usually at the time of delivery rather than early in gestation, it is a disease that should be amenable to prevention. The risk for transmission to the neonate from an infected mother is high (30-50%) among women who acquire a new HSV infection near the time of delivery.[3] Thus, the prevention of acquisition of genital HSV infection during late pregnancy is important for the prevention of neonatal herpes. Among women who acquire genital HSV before the third trimester of pregnancy, the risk of transmission to the neonate is low (< 1%).[3-5] For such mothers, prevention of neonatal herpes depends on avoiding exposure of the infant to recurrent herpetic lesions during delivery.

★ EDITORS' CHOICE ★

Most women (60-80%) who deliver infants with neonatal herpes infection have no signs, symptoms, or history of genital herpes.[4,6] Studies suggest that the risk of neonatal infection tends to be higher in pregnant women who are seronegative for both HSV-1 and -2,[3,5] which reflects the susceptibility for the acquisition of primary HSV infection in late pregnancy.[7] Some specialists recommend screening all pregnant women with type-specific serology tests to identify those women with unrecognized HSV-1 or -2 infections and those women who are still at risk for becoming infected.[8,9] Prevention efforts such as careful examination for herpetic lesions at the onset of labor, with delivery by cesarean section in women with lesions, can then be more focused. For women who are still at risk for the acquisition of HSV during pregnancy, counseling messages aimed at reducing the acquisition of HSV infection in late pregnancy are especially important. We estimated the seroprevalence of HSV-1 and -2 in a national sample of pregnant women in the United States and examined key factors that are associated with HSV-1 infection, HSV-2 infection, and HSV seronegativity. We also projected the rate of neonatal herpes by demographic characteristics of the mothers on the basis of HSV serostatus-specific rates of neonatal herpes from a recent published study.

Materials and Methods

National Health and Nutrition Examination Surveys (NHANES) are a series of cross-sectional national surveys conducted by the National Center for Health Statistics. Details of the survey methods have been published previously.[10] In brief, a nationally representative sample of the US civilian noninstitutionalized population was selected with the use of a complex, stratified, multistage probability sample design. Some populations, such as adolescents, Mexican American women, and pregnant women were oversampled. Persons who were selected

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Received March 7, 2006; accepted July 6, 2006.

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0002-9378/$32.00
Published by Mosby Inc.
doi: 10.1016/j.ajog.2006.07.051

TABLE 1
The distribution by demographic factors in the sample of pregnant women in our analyses (n = 626) and in all women who gave birth in the United States in 2000 (n = 4,058,814)

Demographic variable	Pregnant women in our analyses (%)	All births in the United States in 2000: mothers' characteristics (%)*
Race/ethnicity		
NonHispanic white	57.9	58.2
NonHispanic black	15.3	14.9
Mexican American	13.5	14.3
Other	13.3	12.6
Age ≤ 20 y	13.2	11.8
Education > high school	77.1	78.3

* Data on all births were from the report published by Martin JA, Hamilton BE, Ventura SJ, Menacker F, Park MM. Births: final data for 2000. National vital statistics reports; vol 50, no. 5. Hyattsville (MD): National Center for Health Statistics; 2002.

for the surveys were interviewed and underwent a health examination in mobile examination centers.

In the NHANES conducted from 1999-2002, all persons 14-59 years of age were interviewed about sexual behavior. The questionnaire was administered with audio computer-assisted self-interview in a private room. As part of the survey examination, pregnancy tests (urine and serum) were performed for female participants 12-59 years of age and menstruating girls aged 8-11 years. Only persons aged 14-49 years were tested for HSV antibodies. Of participants aged 14-49 years who were originally selected for the survey, 83% were interviewed, 79% were examined, and 72% were tested for HSV-1 and -2.

Laboratory methods

A rapid chromatographic immunoassay (Icon 25 human chorionic gonadotropin [urine/serum] test kit; Beckman Coulter Inc, Fullerton, CA) was used for qualitative detection of human chorionic gonadotropin in urine and serum. The test uses a combination of monoclonal and polyclonal antibodies to detect selectively elevated levels of human chorionic gonadotropin in urine or serum.

We used purified glycoprotein specific for HSV-1 (gG-1) and HSV-2 (gG-2) antigens to detect type-specific antibodies using the solid-phase enzymatic immunodot assays.[11,12] The performance of the immunodot assays is high, with respect to sensitivity and ability to discriminate between HSV-1 and HSV-2.[11-13]

Statistical analyses

SUDAAN software (release 9.0; Research Triangle Institute, Cary, NC) was used for statistical analyses to account for the complex survey design. All prevalence or seroprevalence estimates were weighted to represent the noninstitutionalized civilian US population and to account for oversampling and nonresponse to the interview and the examination.[14] The standard weights for survey examination published by the National Center for Health Statistics were used for all analyses. Confidence intervals (CIs) for the seroprevalence estimates were calculated based on a log transformation, with the standard error (SE) calculated by the delta method.[15] In NHANES 1999-2002, race/ethnicity categories were defined by self-report as nonHispanic black (NH-black), nonHispanic white (NH-white), and Mexican American. Persons who did not fit into these categories were classified as "Other" and were included in the total population.

RESULTS

In NHANES 1999-2002, a total of 704 women had a positive pregnancy test or reported being pregnant. Of these, 700 women were between 14-49 years of age; HSV serology results were available for 626 women (89%). The reasons for missing HSV serology test results included refusal or unsuccessful venipuncture or the need to use serum for other tests. Pregnant women with and without HSV test results were not statistically different with respect to age, race/ethnicity, or education level.

Among the 626 women with HSV serology results available, the mean age was 27 years (range, 15-41 years). The median number of lifetime sex partners was 4 (mean, 7). The distributions by age, race/ethnicity, and education level in this sample of pregnant women were similar to those in all births in the United States in 2000 (Table 1). Overall, HSV-1 seroprevalence was 63%, HSV-2 seroprevalence was 22%, infection with both HSV-1 and HSV-2 was 13%; and HSV seronegativity was 28%.

In Table 2, we present the seroprevalence of HSV-1 only, HSV-2 (with and without HSV-1), and HSV seronegativity by selected demographic and behavioral factors. Both HSV-1 and HSV-2 seroprevalence varied by race/ethnicity. As a result, NH-white mothers were more likely to be seronegative compared with other racial/ethnic groups (40% vs 11%; $P < .001$). A regression model was fit to find demographic and behavioral factors that were associated independently with HSV-2 infection. All 7 variables in Table 2 were considered in the initial model, and only age, race/ethnicity, and the lifetime number of sex partners were associated independently with HSV-2 infection (all $P < .05$). Marital status, education level, poverty status, and age at first sex were not associated statistically with HSV-2 infection after adjustment for other variables in the model. Similar approaches were used to find factors that were associated with HSV seronegativity, and only race/ethnicity, education level, and the lifetime number of sex partners were associated independently with being HSV-seronegative. On the basis of these analyses, we conclude that race/ethnicity and the lifetime number of sex partners are the best 2 predictors of HSV serostatus in pregnant women in the United States.

TABLE 2
HSV-1 and HSV-2 seroprevalence in NHANES 1999-2002, by demographic and behavioral factors and history of genital herpes

Variable	Sample size (n)	Percentage positive for HSV-1 only (95% CI)	Percentage positive for HSV-2: with or without HSV-1 (95% CI)	Percentage HSV seronegative (95% CI)
Total	626	50 (43-57)	22 (16-31)	28 (22-36)
Age (y)				
≤ 25	303	59 (50-71)	15 (10-24)	25 (16-40)
≥ 26	323	42 (33-54)	28 (18-44)	30 (22-41)
Race/ethnicity				
Mexican American	188	76 (66-87)	17 (10-28)	7 (4-14)*
NonHispanic black	89	38 (27-53)	55 (44-69)	7 (2-26)*
NonHispanic white	287	42 (33-53)	18 (9-33)*	40 (32-50)
Other	62	69 (52-93)	12 (6-25)*	19 (7-52)*
Marital status				
Never married	135	45 (37-56)	32 (22-46)	22 (13-41)
Married	365	55 (46-65)	14 (8-24)	32 (24-42)
Other/unknown	126	39 (29-52)	38 (22-66)	23 (12-44)*
Educational level				
High school or less	339	57 (49-66)	22 (15-33)	21 (12-36)
More than high school	286	44 (34-55)	23 (13-39)	34 (26-43)
Poverty index				
Below poverty level	154	57 (49-67)	30 (23-40)	13 (8-23)
At or above poverty level	417	45 (38-54)	21 (13-32)	34 (26-43)
Age at first sex (y)				
≤ 15	195	53 (44-65)	25 (17-37)	22 (14-34)
≥ 16	367	49 (39-61)	22 (14-36)	29 (22-38)
Lifetime sex partners (n)				
≤ 3	287	58 (50-69)	8 (5-15)	33 (25-45)
≥ 4	261	46 (37-56)	34 (25-48)	20 (13-31)

In some cases, data were not available for all subjects. Statistical significance can be assessed conservatively by a comparison of the CIs surrounding the seroprevalence estimate. The difference in seroprevalence estimates are statistically significant if the CIs do not overlap. For example, HSV-2 seroprevalence differed significantly among women with ≤ 3 lifetime sex partners compared with women with ≥ 4 lifetime sex partners because the 95% CIs surrounding the seroprevalence estimates (5-15%) and (25-48%) did not overlap.

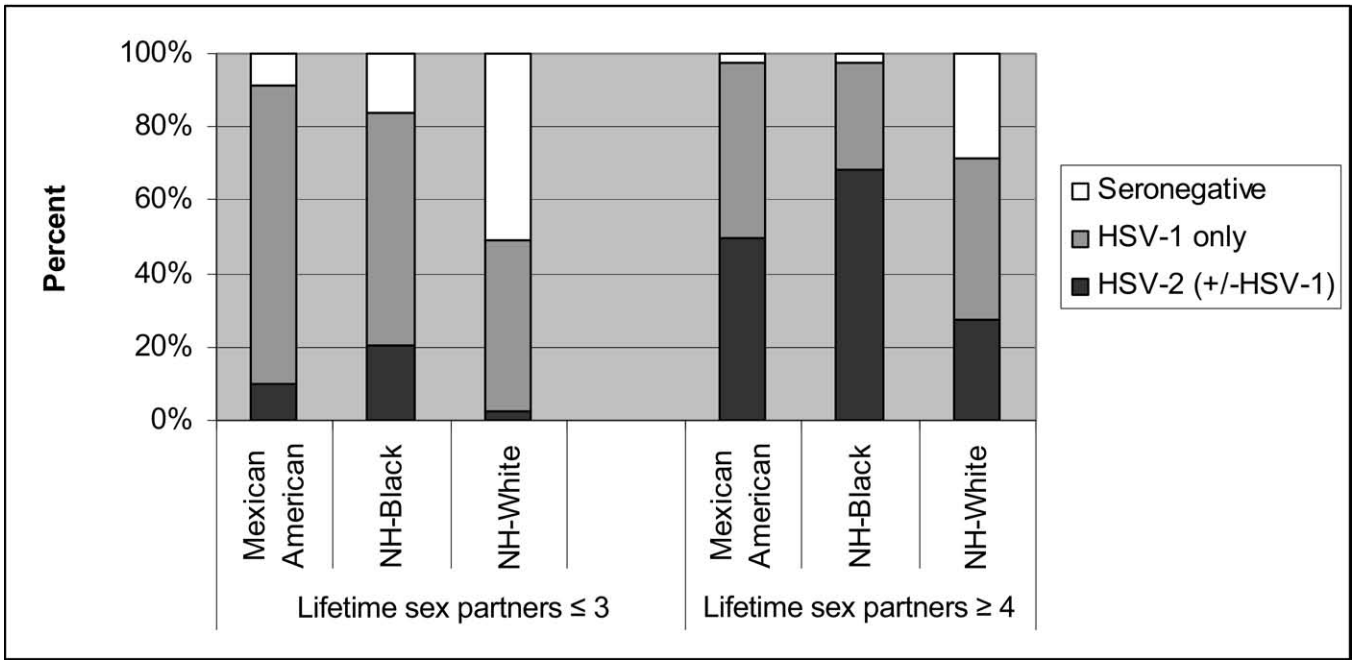
* Estimates may be unreliable because the relative SE is large (SE/seroprevalence > 30%).

In Figure 1, we present HSV serostatus by race/ethnicity and the lifetime number of sex partners. In pregnant women who had ≤ 3 lifetime sex partners, HSV-2 seroprevalence was 10% in Mexican American women, 21% in NH-black women, and 2% in NH-white women. In these women, the prevalence of HSV seronegativity was 9%, 16%, and 51%, respectively. In women with ≥ 4 lifetime sex partners, HSV-2 seroprevalence was 49% in Mexican American women, 68% in NH-black women, and 28% in NH-white women; the prevalence of HSV seronegativity was 28% in NH-white women and only 2% in Mexican American and NH-black women. Although HSV-2 seroprevalence appeared to be higher in women ≥ 26 years of age in all racial/ethnic groups, HSV seropositivity was similar in the 2 age groups within each racial/ethnic group (Figure 2).

Survey participants aged 18-59 years were asked, "Has a doctor or other health care professional ever told you that you had genital herpes?" A total of 517 pregnant women responded to this question, and only 3% answered "yes." Among those who were seropositive for HSV-2, 9% answered "yes" to this question; 2% of women seropositive for HSV-1 only answered "yes."

Serostatus-specific rates of neonatal herpes were estimated from a study of

FIGURE 1
The distribution of HSV infection status according to race/ethnicity and the lifetime number of sex partners in NHANES 1999-2002



NH-Black, NonHispanic blacks; *NH-White*, NonHispanic whites.

approximately 32,000 deliveries during 1982-1999 in the Seattle area.[3] The rate of neonatal herpes infection was 54 per 100,000 live births (95% CI, 19.8-118) among women who were HSV-seronegative, 26 per 100,000 live births (95% CI, 9.3-56) among women who were seropositive for HSV-1 only, and 22 per 100,000 (95% CI, 4.4-64) among women who were seropositive for HSV-2. Applying these serostatus-specific rates to the sample of the pregnant women in our study (Table 2), the projected national rate of neonatal herpes is 33 per 100,000 live births. The projected rate is similar in infants born to Mexican American mothers or NH-black mothers (27 and 26, respectively, per 100,000 live births) and is higher, 36 per 100,000 live births, in infants born to NH-white mothers. Most neonatal herpes cases are projected to occur in infants whose mothers are HSV-seronegative or seropositive for HSV-1 only (Table 3). Overall, the proportion of infants with neonatal herpes who are born to mothers with existing HSV-2 infection is projected to be only 15% (Table 3).

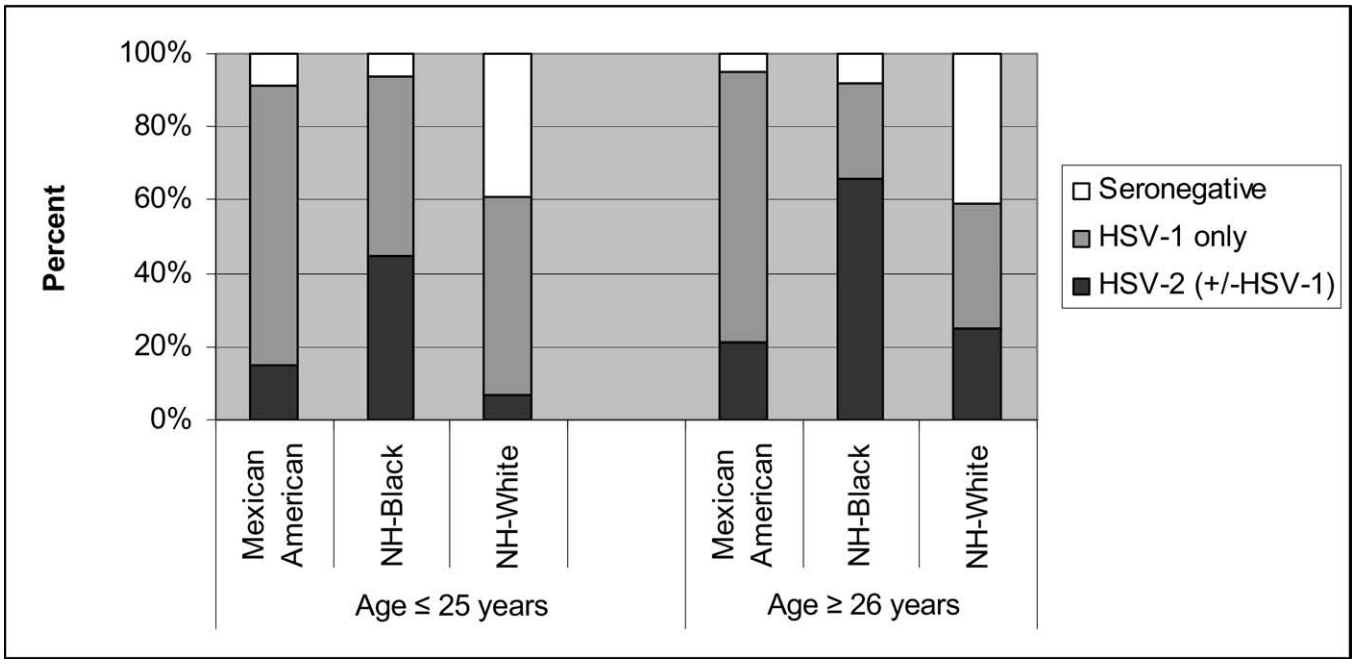
Comment

Our data suggest that, in pregnant women, race/ethnicity and the lifetime number of sex partners are the best predictors for HSV serostatus. In all racial/ethnic groups, the number of lifetime sex partners can better differentiate the mother's serostatus than age. Our findings also suggest that women who are regarded traditionally as low risk for HSV infection may be at elevated risk of transmitting HSV infections to the neonate and that effective prevention efforts for neonatal herpes must emphasize prevention of HSV acquisition in late pregnancy.

Our analyses by race/ethnicity suggest that NH-white women may be at higher risk of transmitting HSV to their infants, mainly because 40% of these women are HSV-seronegative and thus still at risk for acquiring both genital HSV-1 and HSV-2 infections in late pregnancy. In contrast, pregnant women of Mexican American or NH-black race/ethnicity, especially those who have a larger number of lifetime sex partners, are rarely seronegative and thus at lower risk for acquiring genital HSV-1 infection. Although women who are infected with HSV-1 only are still at risk for acquiring genital HSV-2 infection, preexisting HSV-1 antibodies can alleviate clinical manifestations of HSV-2 infection[16,17] and may also reduce the risk of transmitting HSV-2 to the neonate.

The observations that newly acquired maternal HSV infection is more likely than longstanding maternal infection to result in neonatal herpes and that mothers who are seronegative are paradoxically at higher risk to deliver babies in whom neonatal herpes will develop have highlighted the importance of focusing on HSV-seronegative women for intensified prevention efforts. Unlike infections for which effective vaccines are available, optimal prevention strategies for neonatal herpes have not been determined. Careful examination for herpetic lesions at the onset of labor and delivery by cesarean section for women with lesions have been established and accepted as routine prevention recommendations for neonatal herpes.[8] Traditionally, this

FIGURE 2
The distribution of HSV infection status according to race/ethnicity and age in NHANES 1999-2002



NH-Black, NonHispanic black; *NH-White*, NonHispanic white.

prevention strategy has been targeted to pregnant women with known genital herpes. However, most women who are infected with HSV-2 do not know their status. In the recent study in the Seattle area, only 3 of 15 neonatal herpes cases occurred in mothers who were seropositive for HSV-2,[3] even though HSV-2 seroprevalence in pregnant women in the study (with or without HSV-1) was 28%. Using data from the national sample of pregnant women in our study in which HSV-2 seroprevalence was 22%, we projected that only 15% of all neonatal herpes cases would occur in women who acquire HSV-2 before late pregnancy.

The projected national rate of neonatal herpes from our study is consistent with early reports.[3,18,19] Our projected rate was based on the study in the Seattle area, where clinical practices that may affect the rate of neonatal herpes, such as serologic testing during pregnancy, may be practiced more widely than elsewhere. Therefore, the serostatus-specific rates may not be generalizable to the United States in general. One important limitation of our study is that our projected rates of neonatal herpes and the distribu-

TABLE 3
Projected national rates of neonatal herpes by race/ethnicity and the projected distribution of cases by the serostatus of the mother, based on published serostatus-specific rates*

Race/ethnicity	Projected rate of neonatal herpes per 100,000 live births	Projected distribution of neonatal herpes cases by the serostatus of the mother (%)		
		HSV-1 only	HSV-2 (with or without HSV-1)	HSV-seronegative
Overall	33	39	15	46
Mexican American	27	73	14	14
NonHispanic black	26	38	47	15
NonHispanic white	36	30	11	60

The projected rate of neonatal herpes (per 100,000 live births) was calculated with the use of HSV seroprevalence in our study and the rates from the aforementioned study: (HSV-1 only seroprevalence × 26) + (HSV-2 seroprevalence × 22) + (HSV seronegativity × 54). For example, the overall rate = (50% × 26) + (22% × 22) + (28% × 54) = 33. The projected percentage of neonatal herpes by mothers' serostatus was calculated as: (seroprevalence × serostatus-specific rate)/(total projected rate). For example, among all women infected with HSV-1 only, the projected percentage of all neonatal herpes is (50% × 26)/33 = 39%.

* Serostatus specific rates used here were from the study by Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA 2003;289:203-9. The rate of neonatal herpes infection was 54/100,000 live births (95% CI, 19.8-118) among HSV-seronegative women, 26/100,000 live births (95% CI, 9.3-56) among women seropositive for HSV-1 only, and 22/100,000 live births (95% CI, 4.4-64) among women seropositive for HSV-2.

tion of cases by mothers' serostatus were calculated on the basis of 1 study at 1 geographic location. The uncertainty of our projections should be emphasized because of the wide CIs surrounding the rate estimates in that study[3] and the possible heterogeneity in risk across the United States.

Although reliable direct estimates of the national rate of neonatal herpes in the United States are not currently available,[18] even the lower-end estimates of neonatal herpes from previous studies are higher than other congenital and perinatal infections, which include rubella syndrome, gonococcal ophthalmia, HIV infection, and syphilis, for which standard prevention efforts are in place.[18,19] Given that screening pregnant women for HSV infection is still a controversial practice,[8,20] our study suggests that demographic characteristics and sexual history may be helpful in broadly assessing the risk and selecting prevention approaches that are most important. For example, counseling to avoid oral and vaginal sex in the third trimester is probably most important for NH-white women who have few lifetime sex partners, although in NH-black women who have had a larger number of lifetime sex partners careful clinical examination at the onset of labor to reduce the infant's exposure to herpetic lesions may be more important. Future studies are needed to identify clinical services that are feasible and effective to prevent neonatal herpes in pregnant women of various behavioral and demographic characteristics. ■

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