

The New England Journal of Medicine

© Copyright, 1997, by the Massachusetts Medical Society

VOLUME 337

AUGUST 21, 1997

NUMBER 8



THE ACQUISITION OF HERPES SIMPLEX VIRUS DURING PREGNANCY

ZANE A. BROWN, M.D., STACY SELKE, M.A., JUDY ZEH, Ph.D., JEROME KOPELMAN, M.D., ARTHUR MASLOW, M.D., RHODA L. ASHLEY, Ph.D., D. HEATHER WATTS, M.D., SYLVIA BERRY, R.N., MILLIE HERD, R.N., AND LAWRENCE COREY, M.D.

ABSTRACT

Background The acquisition of genital herpes during pregnancy has been associated with spontaneous abortion, prematurity, and congenital and neonatal herpes. The frequency of seroconversion, maternal symptoms of the disease, and the timing of its greatest effect on the outcome of pregnancy have not been systematically studied.

Methods We studied 7046 pregnant women whom serologic tests showed to be at risk for herpes simplex virus (HSV) infection. Serum samples obtained at the first prenatal visit, at approximately 16 and 24 weeks, and during labor were tested for antibodies to HSV types 1 and 2 (HSV-1 and HSV-2) by the Western blot assay, and the results were correlated with the occurrence of antenatal genital infections.

Results Ninety-four of the women became seropositive for HSV; 34 of the 94 women (36 percent) had symptoms consistent with herpes infection. Women who were initially seronegative for both HSV-1 and HSV-2 had an estimated chance of seroconversion for either virus of 3.7 percent; those who were initially seropositive only for HSV-1 had an estimated chance of HSV-2 seroconversion of 1.7 percent; and those who were initially HSV-2-seropositive had an estimated chance of zero for acquiring HSV-1 infection. Among the 60 of the 94 pregnancies for which the time of acquisition of HSV infection was known, 30 percent of the infections occurred in the first trimester, 30 percent in the second, and 40 percent in the third. HSV seroconversion completed by the time of labor was not associated with an increase in neonatal morbidity or with any cases of congenital herpes infection. However, among the infants born to nine women who acquired genital HSV infection shortly before labor, neonatal HSV infection occurred in four infants, of whom one died.

Conclusions Two percent or more of susceptible women acquire HSV infection during pregnancy. Acquisition of infection with seroconversion completed before labor does not appear to affect the outcome of pregnancy, but infection acquired near the time of labor is associated with neonatal herpes and perinatal morbidity. (N Engl J Med 1997;337:509-15.)

©1997, Massachusetts Medical Society.

THE prevalence of genital infection with herpes simplex virus (HSV) and its most serious complication, neonatal herpes, has increased during the past two decades.¹⁻⁶ Neonatal HSV infection most commonly results from contact between the newborn and either HSV type 1 (HSV-1) or HSV type 2 (HSV-2) that is present in the birth canal of an asymptomatic mother during labor and delivery.⁷⁻⁹ The consequences of neonatal infection with HSV are frequently catastrophic; death of the infected neonate or severe neurodevelopmental disability is common.¹⁰ HSV can be asymptotically present in the genital tract at the time of labor as a consequence of the reactivation of disease or the acquisition of genital herpes during pregnancy.^{8,9,11}

Previous studies have suggested that genital HSV infection acquired during pregnancy is associated with preterm labor, intrauterine growth retardation, and spontaneous abortion.^{7,12,13} However, there have been few prospective studies of the frequency and consequences of genital HSV infection acquired at different times during pregnancy. Therefore, we used serologic and virologic methods to study the acquisition of HSV infection among pregnant women.

METHODS

Subjects, Setting, and Procedures

We obtained serum samples at the first prenatal visit and at the time of labor to test for the presence of antibodies against HSV-1 and HSV-2 in 8538 women receiving prenatal care at University Hospital in Seattle between January 1989 and December 1993 and at Madigan Army Hospital in Tacoma between August 1990 and December 1993. In addition, serum samples obtained for routine prenatal tests at 14 to 18 weeks and at 24 to 28 weeks of gestation

From the Departments of Obstetrics and Gynecology (Z.A.B., D.H.W., S.B.), Laboratory Medicine (S.S., R.L.A., L.C.), Statistics (J.Z.), and Medicine (L.C.), University of Washington, Seattle; and the Department of Obstetrics and Gynecology, Madigan Army Medical Center, Tacoma, Wash. (J.K., A.M., M.H.). Address reprint requests to Dr. Brown at Box 356460, University of Washington, Seattle, WA 98195-6460.

were saved and tested when indicated to define more precisely the time of seroconversion. When the women entered the labor room, swabs for culture of HSV were obtained from the external genitalia and cervix.⁸ Isolation and typing of HSV were performed as previously described.¹⁴ Infants born to women from whom HSV was isolated during labor were enrolled in ongoing studies.⁷

Antibodies to HSV-1 and HSV-2 were detected by Western blot assays.¹⁵⁻¹⁹ All serum samples from an individual woman were analyzed simultaneously. For all women whose initial serum sample was positive for HSV-1 but in whom antibodies to HSV-2 later developed, seroconversion was confirmed by absorption-blots assay.¹⁹ The medical records of all women who became seropositive for HSV-1 or HSV-2 were reviewed for symptoms of genital HSV during pregnancy.

Consent was obtained for the appropriate portions of the study protocol, including the review of medical records and the follow-up of infants, according to the guidelines of the human-subjects review board of the University of Washington.

Definitions

Seroconversion was defined as the appearance of antibodies to HSV in the serum sample obtained at the time of labor that were not present at the initial prenatal visit.²⁰⁻²³ This change indicates that HSV was acquired long enough before delivery to permit the development of antibodies to HSV, a process that usually requires four to six weeks. Primary HSV infection was considered to have occurred when there were no detectable antibodies to HSV in the first prenatal serum sample but antibodies to either HSV-1 or HSV-2 were found in the sample obtained at the time of labor. A non-primary first episode was defined as the presence of antibodies to HSV-1 in the initial prenatal serum sample, with antibodies to both HSV-1 and HSV-2 in the sample obtained at the time of labor. No woman who had antibodies to HSV-2 in the initial prenatal serum sample had antibodies to both HSV-2 and HSV-1 in the sample obtained at the time of delivery.

Among women with symptomatic disease, the date of acquisition of genital HSV infection was defined as the date of the first reported genital lesions. Among those with subclinical disease, the date of infection was defined as the midpoint between the time of the negative test for the particular HSV antibody and the time of the first positive antibody test. Infection was considered subclinical if a review of the woman's obstetrical records did not indicate any evidence of vulvovaginitis during pregnancy. The first trimester was defined as the period from conception to 12 completed weeks of gestation, the second trimester as that from the beginning of week 13 through week 28, and the third trimester as that from the beginning of week 29 to the onset of labor. Premature labor was defined as labor occurring before 259 days, or 37 weeks, from the first day of the woman's last menstrual period.²⁴

Statistical Analysis

The frequency of seroconversion was calculated as the ratio of the number of women who had HSV seroconversion to the number at risk for seroconversion. Because the mean interval between the first prenatal visit and the onset of labor was less than the length of a normal pregnancy, the frequency of seroconversion was adjusted for a 40-week gestation period on the assumption that the rate of seroconversion was uniform throughout pregnancy. This method may result in the underestimation of the true frequency of seroconversion because the interval between conception and the first prenatal visit may be a period of normal or increased sexual activity that then declines as pregnancy progresses.²⁵

Categorical variables were compared between groups by means of the chi-square or Fisher's exact test. Rates of seroconversion were compared by permutation tests.²⁶ Standard errors for these rates were estimated with bootstrap resampling.²⁷ Two-group comparisons of distributions of continuous variables were performed by Mann-Whitney tests. All statistical tests were two-sided. Odds ratios for seroconversion, with 95 percent confidence intervals, were estimated from the results of logistic-regression

analyses. Odds ratios indicating the influence of demographic variables on the rate of seroconversion were estimated by multivariate analysis. Odds ratios for behavioral variables came from univariate analyses, because missing data greatly reduced the number of women who could be included in a multivariate analysis incorporating these variables.

RESULTS

Characteristics of the Study Population

Of the 17,125 women who delivered babies at the two study hospitals, 15,434 (90 percent) had serologic testing for HSV at the time of labor. Serum samples obtained during labor were not available from 1691 women (10 percent) because of oversight on the part of physicians, lost specimens, or the women's refusal to allow blood sampling. Serum samples from the first prenatal visit were available for 8538 of the 15,434 women (55 percent). Serum samples were not obtained at the first prenatal visit for 6896 women because the women were referred to the study centers within 30 days of delivery (26 percent of those with missing prenatal samples), no prenatal care was received (7 percent), or prenatal care was received elsewhere (22 percent). In addition, 16 percent of women had already had their initial prenatal visit when we began the study and were thus ineligible for enrollment. The remaining 29 percent of the women with missing prenatal samples either registered for care late in pregnancy, declined to have blood drawn, or did not have the serologic tests because of the physician's oversight.

The demographic characteristics and HSV serologic status of the 8538 women from whom serum samples were obtained both at the first prenatal visit and at the time of labor were similar to those of the 6896 women for whom results of serologic testing for HSV were available only at the time of labor.

Frequency of Antenatal Seroconversion

At entry, 2033 of the 8538 women (24 percent) were HSV-negative; 4074 (48 percent) were seropositive for HSV-1; 939 (11 percent) were seropositive for HSV-2; and 1492 (17 percent) were seropositive for both HSV-1 and HSV-2. Of the 7046 women (83 percent) in whom serologic tests showed susceptibility to HSV infection during pregnancy, 94 (1.3 percent) became seropositive for HSV-1 or HSV-2; 64 (68 percent) acquired antibodies to HSV-2, and 30 (32 percent) acquired antibodies to HSV-1 before the onset of labor (Table 1). The median interval between the first prenatal HSV test and the HSV test at the time of labor was 196 days (range, 26 to 280) for the entire study group and 202 days (range, 26 to 257) for the 94 women in whom seroconversion occurred.

The estimated rate of seroconversion during pregnancy, adjusted for a 40-week gestation, was 2.1 percent. The adjusted rate of seroconversion among the

TABLE 1. FREQUENCY OF ANTENATAL HSV SEROCONVERSION AMONG 7046 INITIALLY HSV-SUSCEPTIBLE WOMEN.

TYPE OF SEROCONVERSION	NO. WITH SEROCONVERSION/ NO. AT RISK*	OBSERVED RATE	ADJUSTED RATE†
			percent
Any seroconversion	94/7046	1.3	2.1±0.2
HSV-negative to HSV-1-positive or HSV-2-positive	49/2033	2.4	3.7±0.5
HSV-negative to HSV-1-positive	30/2033	1.5	2.3±0.4
HSV-negative to HSV-2-positive	19/2033	0.9	1.4±0.3
HSV-1-positive to HSV-1-positive and HSV-2-positive	45/4074	1.1	1.7±0.3
HSV-2-positive to HSV-1-positive and HSV-2-positive	0/939	0	0

*The median period of observation was 202 days.

†The adjusted rate is the estimated mean (±SE) chance of seroconversion adjusted for 280 days of gestation and is based on the assumption of a uniform rate of seroconversion during the entire pregnancy.

TABLE 2. FREQUENCY OF SYMPTOMS AND TRIMESTER OF INFECTION AMONG WOMEN WITH HSV SEROCONVERSION DURING PREGNANCY.

CATEGORY	SYMPTOMATIC SEROCONVERSION	SUBCLINICAL SEROCONVERSION	TOTAL
		number (percent)	
All women with seroconversion	34 (36)	60 (64)	94 (100)
Type of seroconversion			
HSV-negative to HSV-1-positive	8 (24)*	22 (37)	30 (32)
HSV-negative to HSV-2-positive	8 (24)	11 (18)	19 (20)
HSV-1-positive to HSV-1-positive and HSV-2-positive	18 (53)	27 (45)	45 (48)
Trimester of infection			
First	7 (21)	11 (18)	18 (19)
Second	15 (44)	3 (5)	18 (19)
Third	12 (35)	12 (20)	24 (26)
First or second†	0	3 (5)	3 (3)
Second or third‡	0	22 (37)	22 (23)
Unknown	0	9 (15)	9 (10)

*Two women had oral symptoms only, two had oral and genital symptoms, and four had genital symptoms only.

†Serum samples were obtained at the initial prenatal visit, at 26 weeks, and at the time of labor.

‡Serum samples were obtained at the initial prenatal visit, at 16 weeks, and at the time of labor.

initially HSV-seronegative women was 3.7 percent; among those who were initially HSV-1-seropositive, 1.7 percent became HSV-2-seropositive. Although the rates of HSV-2 seroconversion among initially HSV-seronegative women were similar to those among HSV-1-seropositive women (1.4 percent vs. 1.7 percent), the rate of HSV-1 seroconversion among those who were HSV-seronegative was significantly higher than that among those who were HSV-2-seropositive (2.3 percent vs. 0, $P=0.001$), suggesting that prior HSV-2 infection prevented the acquisition of HSV-1 (Table 1).

Frequency of Subclinical and Clinical HSV Infection

Among the 94 women who became HSV-seropositive during the prenatal period, 60 (64 percent) had subclinical infections (Table 2). The frequency of subclinical seroconversion was similar among those who acquired HSV-1 (22 of 30 [73 percent]) and those who acquired HSV-2 (38 of 64 [59 percent]). All 26 women with clinical symptoms of HSV-2 infection and 6 of 8 with symptomatic HSV-1 infection had genital lesions. Overall, 32 of the 34 women who had seroconversion and symptomatic infection had genital infections; 4 received antiviral therapy.

TABLE 3. DEMOGRAPHIC AND BEHAVIORAL CHARACTERISTICS OF WOMEN WHO HAD HSV SEROCONVERSION AND WOMEN WITH SIMILAR SEROLOGIC PROFILES WHO DID NOT HAVE SEROCONVERSION.

CHARACTERISTIC	INITIALLY HSV-SERONEGATIVE			INITIALLY HSV-1-SEROPOSITIVE		
	SEROCONVERSION (N=49)*	NO SEROCONVERSION (N=1983)	ODDS RATIO (95% CI)†	SEROCONVERSION (N=45)‡	NO SEROCONVERSION (N=4026)	ODDS RATIO (95% CI)†
Demographic						
Mean age (yr)	22	24	0.9 (0.9–1.0)	24	25	1.0 (0.9–1.0)
Race (%)						
White	82	80	1.0	49	59	1.0
Black	12	11	0.7 (0.3–1.8)	27	16	1.7 (0.8–3.6)
Other	6	9	0.6 (0.2–1.9)	24	25	1.1 (0.5–2.3)
Married (%)	51	73	0.6 (0.3–1.1)	49	68	0.5 (0.3–1.0)
Primigravida (%)	49	37	1.2 (0.6–2.2)	36	28	1.3 (0.7–2.4)
Behavioral						
Smoking (%)	33	25	1.5 (0.8–2.8)	29	28	1.1 (0.6–2.1)
Alcohol use (%)	19	15	1.3 (0.6–2.8)	13	13	1.0 (0.4–2.4)
Illicit-drug use (%)	10	5	2.2 (0.8–5.6)	9	8	1.2 (0.4–3.5)
Any sexually transmitted disease (%)	51	33	2.1 (1.2–3.8)	66	34	3.9 (2.1–7.4)

*For this group, seroconversion denotes positivity for HSV-1 or HSV-2.

†For demographic characteristics, the adjusted odds ratios with 95 percent confidence intervals (CIs) from the multivariate logistic-regression analysis give the odds of prenatal seroconversion among the women who had seroconversion before delivery or not at all. The odds ratio for age is that associated with being one year older, assuming that other demographic characteristics are the same. For race, the odds ratio is shown in comparison with white race (odds ratio=1.0). For dichotomous variables (e.g., married vs. unmarried or smoking vs. no smoking), the reference category is not shown. For behavioral characteristics, the odds ratios with 95 percent confidence intervals were obtained from univariate logistic regressions.

‡For this group, seroconversion denotes positivity for both HSV-1 and HSV-2.

Time of Acquisition of HSV

Of the 34 women with symptomatic infection, 7 (21 percent) acquired HSV in the first trimester, 15 (44 percent) in the second, and 12 (35 percent) in the third. Of the 60 women with subclinical HSV, 11 (18 percent) were infected in the first trimester, 3 (5 percent) in the second, and 12 (20 percent) in the third (Table 2). In three women, infection was known only to have occurred in the first or second trimester. In 22 women, infection occurred in the second or third trimester. In nine women, interim serum samples were not available to permit us to identify the trimester of HSV infection. Thus, of the 60 women in whom the trimester of infection was known, 18 (30 percent) acquired HSV infection in the first trimester, 18 (30 percent) in the second, and 24 (40 percent) in the third.

Demographic, Behavioral, and Obstetrical Characteristics of the Women with Seroconversion

We compared the demographic, behavioral, and obstetrical characteristics of the 94 women who had HSV seroconversion with those of 6009 women who did not have seroconversion (Table 3). In addition, the 49 initially HSV-seronegative women who became seropositive for HSV-1 or HSV-2 and 45 HSV-1-seropositive women who became seropositive for HSV-2 were compared with HSV-seronega-

tive women who remained HSV-seronegative and HSV-1-seropositive women who did not acquire HSV-2. Younger age, not being married, and the occurrence of other sexually transmitted diseases were associated with seroconversion.

Overall, 25 of the 94 women who became seropositive for HSV during pregnancy (27 percent) underwent a cesarean section (6 because of the presence of active genital lesions), as compared with 17 percent of the women who did not have seroconversion ($P=0.02$). Among the 32 women who acquired symptomatic genital HSV during pregnancy, 10 (31 percent) delivered their infants by cesarean section; 6 of these women had active, recurrent genital lesions at the time of delivery. Among the 60 women who acquired subclinical HSV infection, 15 (25 percent) delivered by cesarean section. The frequency with which fetal-scalp electrodes and intrauterine pressure catheters were used during labor and delivery was similar among the 94 women who had seroconversion (56 percent and 52 percent, respectively) and the 6009 women who did not (62 percent and 50 percent).

Effects of Seroconversion to HSV Positivity on Neonates

There were no significant differences in the frequency of complications between the 94 infants born to mothers who had HSV seroconversion and

TABLE 4. OUTCOME OF PREGNANCY AMONG WOMEN WHO HAD SEROCONVERSION AS COMPARED WITH WOMEN WITH SIMILAR SEROLOGIC PROFILES WHO DID NOT HAVE SEROCONVERSION.

CHARACTERISTIC	MOTHER INITIALLY HSV-SERONEGATIVE			MOTHER INITIALLY HSV-1-SEROPOSITIVE		
	SEROCONVERSION (N = 49)*	NO SEROCONVERSION (N = 1983)	P VALUE†	SEROCONVERSION (N = 45)‡	NO SEROCONVERSION (N = 4026)	P VALUE†
Newborn						
Median birth weight — g	3289	3400	0.22	3470	3350	0.13
Median gestational age — wk	39	40	0.27	40	39	0.41
Delivered at <37 wk — %	4	13	0.11	4	13	0.15
Median head circumference — cm	34	34	0.33	35	34	0.63
Median length — cm	50	51	0.11	51	50	0.86
Pregnancy outcome§			0.89¶			0.55
Spontaneous abortion — no. (%)	1 (2)	23 (1.2)		1 (2)	39 (1.0)	
Stillbirth — no. (%)	1 (2)	11 (0.6)		0	43 (1.1)	
Neonatal death — no. (%)	0	38 (1.9)		0	76 (1.9)	
Live birth and neonatal survival — no. (%)	47 (96)	1879 (96)		44 (98)	3817 (96)	

*For this group, seroconversion denotes positivity for HSV-1 or HSV-2.

†P values for pregnancy outcomes are based on an assumed normal distribution of the log odds ratio. The odds ratio estimates the relative risk of an adverse pregnancy outcome among women who had seroconversion as compared with those who did not. The other P values are from chi-square or Mann-Whitney tests.

‡For this group, seroconversion denotes positivity for both HSV-1 and HSV-2.

§The numbers of pregnancy outcomes do not equal the totals for the groups, because of missing data.

¶The estimated relative risk of an adverse outcome of pregnancy for women who were initially HSV-negative and had seroconversion for HSV-1 or HSV-2 during pregnancy, as compared with women who remained HSV-seronegative, was 1.1 (95 percent confidence interval, 0.3 to 4.7).

||The estimated relative risk of an adverse outcome of pregnancy for women who were initially HSV-1-seropositive and who had HSV-2 seroconversion during pregnancy, as compared with women who remained seropositive only for HSV-1, was 0.5 (95 percent confidence interval, 0.1 to 4.0).

the infants of the 6009 women who did not seroconvert (Table 4). There were no cases of herpes among the neonates of the 94 women who seroconverted. On the basis of a binomial probability calculation, we are 95 percent confident that the chance that a woman who becomes seropositive during pregnancy will infect her newborn with HSV is less than 3.2 percent. Of the 94 women with seroconversion, cultures for HSV were performed at the time of labor in 71. Of these, five (7 percent) were positive.

Relation of Neonatal Herpes to Initial Episodes of Genital HSV at the Time of Labor

Nine women acquired a genital HSV infection near the onset of labor, five of whom had lesions at the time of labor (Table 5). Since they had not completed HSV seroconversion by the time of labor, they were excluded from the main study cohort. During labor, all had either no detectable antibodies to HSV or antibodies that were different from the HSV type isolated from the genitalia. Serologic and virologic evidence indicated that seven of these nine women had a non-primary first episode of HSV-2 infection and the other two had a primary genital HSV-1 infection.

Neonatal HSV infection developed in four of the nine infants born to these women — both of the in-

fants born to mothers who had primary genital HSV-1 and two of the seven born to mothers with non-primary first episodes of infection (Table 5). The frequency of neonatal HSV infection was significantly higher among the infants of women with first episodes of HSV near the time of labor (4 of 9) than among those born to women who acquired their infection earlier and had seroconversion before the onset of labor (0 of 94, $P < 0.001$).

DISCUSSION

We estimate that HSV was acquired by 2 percent or more of susceptible women during pregnancy. Among the infants of 94 women who became seropositive for HSV before labor, there were no cases of neonatal herpes or any increase in pregnancy-related morbidity. However, among the infants born to nine women who acquired HSV infection at or near the time of labor, neonatal HSV developed in four, of whom one died and one had long-term neurologic sequelae.

The absence of definable morbidity in association with HSV seroconversion before the onset of labor is comforting and yet surprising. Previous studies have demonstrated an association between first episodes of genital HSV infection and preterm labor, intrauterine growth retardation, and spontaneous abortion.^{7,12,13} These observations have all come from

TABLE 5. CHARACTERISTICS OF HSV INFECTION ACQUIRED NEAR THE TIME OF LABOR AND NEONATAL OUTCOME.

PATIENT NO.	PRENATAL SEROLOGIC STATUS*	SEROLOGIC STATUS DURING LABOR	HSV TYPE ISOLATED DURING LABOR	SYMPTOMS AT SEROCONVERSION	GESTATIONAL AGE AT DELIVERY (WK)	VAGINAL DELIVERY	LESIONS AT DELIVERY	NEONATAL HERPES IN INFANT	DEVELOPMENTAL DISABILITY IN INFANT
1	Negative	Negative	HSV-1†	Yes	38	Yes	No†	Yes	Unknown
2	NA	Negative	HSV-1	No	33	Yes	No	Yes	No
3	NA	HSV-1-positive	HSV-2	Yes	37	Yes	No‡	Yes	Yes
4	NA	HSV-1-positive	HSV-2	Yes	40	Yes	No§	No	No
5	HSV-1-positive	HSV-1-positive	HSV-2	No	41	Yes	No	No	No
6	NA	HSV-1-positive	HSV-2	No	41	Yes	No	No	No
7	HSV-1-positive	HSV-1-positive	HSV-2	Yes	40	Yes	No¶	No	No
8	NA	HSV-1-positive	HSV-2	Yes	26	Yes	Yes	Yes	Died
9	HSV-1-positive	HSV-1-positive	HSV-2	No	40	Yes	No	No	No

*NA denotes not available because the women received no prenatal care or received prenatal care at another institution.

†Because lesions were reported six days post partum, cultures were not obtained at the time of labor. HSV-1 infection was assumed on the basis of the partner's HSV-1 status.

‡Lesions were reported eight days post partum.

§Lesions were reported 14 days before delivery; no lesions were evident on the cervix or labia at the onset of labor.

¶Lesions were reported 22 days before delivery; none were observed on the day of delivery.

||The woman received no prenatal care; she was admitted with complete dilatation, with the infant in breech presentation, and a 1-cm lesion on the right labium.

studies based on cultures and serologic tests performed at the time of labor. We studied seroconversion prospectively during pregnancy in a large, well-defined cohort, comparing pregnancy outcomes among women with and without seroconversion. Although our study involved more than 8000 women and 94 cases of HSV seroconversion, the frequency of complications of pregnancy was low both among women who had seroconversion and among those who did not. Thus, it is possible that HSV may have some effect on pregnancy that could be demonstrated only by larger cohort studies.

Of 60 women for whom we could identify the trimester when HSV was acquired, 30 percent became infected in the first trimester, 30 percent in the second, and 40 percent in the third — suggesting that the risk of acquisition is relatively uniform during pregnancy. However, since the frequency of coitus is higher in early pregnancy and declines thereafter, the actual risk of HSV seroconversion may decline as the pregnancy advances.²⁵

Among the eight women in whom seroconversion to HSV-1-positivity was accompanied by clinical symptoms, six had genital lesions and two had only oropharyngeal lesions. Several studies have demonstrated an increase in the prevalence of genital HSV-1 in recent years, especially among patients with recently acquired HSV infection.^{1,2,6,19,20} Perhaps this increase results from a perception among young couples that oral-genital sex is "safe."

The two cases of neonatal HSV-1 infection underscore the importance of recognizing that neonatal herpes can result from infection with either viral sub-

type and that the prevention of genital HSV-1 infection in the third trimester is important in terms of the health of the neonate. Lastly, although 7 percent of the infants born to mothers who became HSV-seropositive before the onset of labor but had subclinical viral shedding at the time of labor were exposed to HSV during delivery, none acquired HSV infection. In contrast, four of the nine infants born to mothers who lacked type-specific antibodies to the homologous virus acquired HSV infections. This finding underscores the potential role of type-specific antibodies in protecting against HSV transmission.

The absence of discernible perinatal morbidity among the babies born to women in whom seroconversion occurred during pregnancy suggests that routine antiviral chemotherapy may not be necessary for women who acquire HSV well before the onset of labor. Selected women who are highly symptomatic or in whom there is evidence of disseminated infection may require antiviral chemotherapy. Cases such as these were extremely uncommon in our study population.

Our study also suggests that efforts to reduce the high morbidity associated with neonatal HSV infection should be concentrated on preventing the maternal acquisition of HSV infection in the latter part of pregnancy. Serologic testing for HSV in the latter half of pregnancy could identify women who are susceptible to HSV infection, so that serologic testing of their partners and appropriate counseling as to the risk of acquiring genital herpes could be undertaken. Such counseling should promote awareness of the risk of acquiring genital HSV-1 infection

from oral–genital contact among those who are seronegative for both HSV-1 and HSV-2. Abstinence from intercourse or the use of condoms during the last trimester could also be recommended when the woman is at risk for acquiring HSV-1 or HSV-2.

Supported by a grant (AI-30731) from the National Institute of Allergy and Infectious Diseases.

The opinions expressed in this article are solely those of the authors and do not necessarily reflect those of the Department of the Army or the Department of Defense.

REFERENCES

1. Tayal SC, Pattman RS. High prevalence of herpes simplex virus type 1 in female anogenital herpes simplex in Newcastle upon Tyne 1983-92. *Int J STD AIDS* 1994;5:359-61.
2. Ross JD, Smith IW, Elton RA. The epidemiology of herpes simplex virus types 1 and 2 infection of the genital tract in Edinburgh 1978-1991. *Genitourin Med* 1993;69:381-3.
3. De Schryver A, Meheus A. Epidemiology of sexually transmitted diseases: the global picture. *Bull World Health Organ* 1990;68:639-54.
4. Whitley RJ. Herpes simplex virus infections of women and their offspring: implications for a developed society. *Proc Natl Acad Sci U S A* 1994;91:2441-7.
5. Johnson RE, Nahmias AJ, Magder LS, Lee FK, Brooks CA, Snowden CB. A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. *N Engl J Med* 1989;321:7-12.
6. Corey L. The current trend in genital herpes: progress in prevention. *Sex Transm Dis* 1994;21:Suppl:S38-S44.
7. Whitley R, Arvin A, Prober C, et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. *N Engl J Med* 1991;324:450-4.
8. Brown ZA, Benedetti J, Ashley R, et al. Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labor. *N Engl J Med* 1991;324:1247-52.
9. Prober CG, Hensleigh PA, Boucher FD, Yasukawa LL, Au DS, Arvin AM. Use of viral cultures at delivery to identify neonates exposed to herpes simplex virus. *N Engl J Med* 1988;318:887-91.
10. Corey L, Whitley RJ, Stone EF, Mohan K. Difference between herpes simplex virus type 1 and type 2 neonatal encephalitis in neurological outcome. *Lancet* 1988;1:1-4.
11. Wald A, Zeh J, Selke S, Ashley RL, Corey L. Virologic characteristics of subclinical and symptomatic genital herpes infections. *N Engl J Med* 1995;333:770-5.
12. Brown ZA, Benedetti J, Selke S, Ashley R, Watts DH, Corey L. Asymptomatic maternal shedding of herpes simplex virus at the onset of labor: relationship to preterm labor. *Obstet Gynecol* 1996;87:483-8.
13. Brown ZA, Vontver LA, Benedetti J, et al. Effects on infants of a first episode of genital herpes during pregnancy. *N Engl J Med* 1987;317:1246-51.
14. Lafferty WE, Krofft S, Remington M, et al. Diagnosis of herpes simplex virus by direct immunofluorescence and viral isolation from samples of external genital lesions in a high-prevalence population. *J Clin Microbiol* 1987;25:323-6.
15. Ashley RL, Militoni J, Lee F, Nahmias A, Corey L. Comparison of Western blot (immunoblot) and glycoprotein G-specific immunodot enzyme assay for detecting antibodies to herpes simplex virus types 1 and 2 in human sera. *J Clin Microbiol* 1988;26:662-7.
16. Ashley RL, Cent A, Maggs V, Nahmias A, Corey L. Inability of enzyme immunoassays to discriminate between infections with herpes simplex virus types 1 and 2. *Ann Intern Med* 1991;115:520-6.
17. Safrin S, Arvin A, Mills J, Ashley R. Comparison of the Western immunoblot assay and a glycoprotein G enzyme immunoassay for detection of serum antibodies to herpes simplex virus type 2 in patients with AIDS. *J Clin Microbiol* 1992;30:1312-4.
18. Sullender WM, Yasukawa LL, Schwartz M, et al. Type-specific antibodies to herpes simplex virus type 2 (HSV-2) glycoprotein G in pregnant women, infants exposed to maternal HSV-2 infection at delivery, and infants with neonatal herpes. *J Infect Dis* 1988;157:164-71.
19. Ashley RL. Current concepts of laboratory diagnosis of herpes simplex infection. In: Sacks SL, Whitley RJ, Straus SE, eds. *Clinical management of herpesvirus infections*. Washington, D.C.: IOS Press, 1995:137-71.
20. Prober CG, Corey L, Brown ZA, et al. The management of pregnancies complicated by genital infections with herpes simplex virus. *Clin Infect Dis* 1992;15:1031-8.
21. Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med* 1983;98:958-72.
22. Mertz GJ, Ashley R, Burke RL, et al. Double-blind, placebo-controlled trial of a herpes simplex virus type 2 glycoprotein vaccine in persons at high risk for genital herpes infection. *J Infect Dis* 1990;161:653-60.
23. Ashley RL. Laboratory techniques in the diagnosis of herpes simplex infection. *Genitourin Med* 1993;69:174-83.
24. Iams JD. Preterm birth. In: Gabbe SG, Niebyl JR, Simpson JL, eds. *Obstetrics: normal and problem pregnancies*. 3rd ed. New York: Churchill Livingstone, 1996:743.
25. Pepe F, Iachello R, Panella M, et al. Parity and sexual behavior in pregnancy. *Clin Exp Obstet Gynecol* 1987;14:60-5.
26. Edgington ES. *Randomization tests*. New York: Marcel Dekker, 1980.
27. Efron B. *The Jackknife, the Bootstrap, and other resampling plans*. Philadelphia: Society for Industrial and Applied Mathematics, 1982.