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ACCEPTANCE OF HSV TESTING PARTNERS OF HSV-2 SERONEGATIVE PREGNANT WOMEN

Carolyn Gardella, MD, MPH¹, Elizabeth Krantz, MS³, Constance Daruthayan¹, Linda Drolette, BS³, Lawrence Corey, MD^{2,3,5}, and Anna Wald, MD, MPH^{2,3,4}

¹Department of Obstetrics & Gynecology, University of Washington, Seattle WA 98195

²Department of Laboratory Medicine, University of Washington, Seattle WA 98195

³Department of Medicine, University of Washington, Seattle WA 98195

⁴Department of Epidemiology, University of Washington, Seattle WA 98195,

⁵Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, Seattle, WA 98109.

Abstract

Objectives—To estimate the acceptance of HSV testing partners of HSV seronegative pregnant women and identify associated factors.

Study Design—Consecutive women identified as HSV-2 seronegative during routine testing in pregnancy were asked to invite their partners for HSV testing to identify serodiscordance. Logistic regression identified factors associated with partner testing.

Results—Between 2001–2006, 315 women enrolled (28% of those approached) and 242 (77%) partners were tested. Married couples were most likely to be tested (aOR 7.72, 95% CI: 2.47–24.15). Partners of African-American women (aOR 0.17, 95% CI: 0.04–0.71), and those with at least a college degree (aOR 0.43, 95% CI: 0.19–0.98) were less likely to be tested.

Conclusions—In this population, partner testing among HSV-2 seronegative women was feasible which supports further study to determine if identification of partners who pose a potential risk of HSV infection during pregnancy is an effective approach to reduce HSV acquisition in pregnant women.

Keywords

herpes; partner; serologic testing; pregnancy; neonate

Neonatal herpes is a relatively rare infection but can result in long-term disability or death in about half of infected infants.(1) The incidence of neonatal herpes in the United States is difficult to establish. Neonatal herpes is not a reportable disease in most states, and the estimates vary depending on the population and the study methods.(2) Estimates range from 4/100,000 live births derived from passive surveillance of 50 states (3), to 76/100,000 live births from a retrospective cohort study from a large health maintenance organization.(4) In the largest

Correspondence: Carolyn Gardella, MD, MPH University of Washington Department of Obstetrics & Gynecology Box 356460 Seattle, WA 98195 Phone: 206-543-2685, FAX: 206 543-3915 email: cgardel@u.washington.edu..

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Precis: Among HSV-2 seronegative prenatal patients, 77% of partners underwent HSV serologic testing.

prospective study of neonatal herpes, the incidence was 30.1/100,000 live births in the Northwest.(5)

Ninety percent of cases of neonatal herpes occur from exposure to HSV in the maternal genital tract at the time of vaginal delivery. (1,6) A main risk factor for neonatal herpes is maternal acquisition of genital HSV near the time of delivery; acquisition of HSV is associated with a 60-fold higher risk of infection compared with women with established genital herpes. Because of this high relative risk, 60-80% of infants with neonatal herpes are born to women who acquired HSV at the end of pregnancy. (5) Thus, prevention strategies must include women at risk for HSV infection in pregnancy in their target population to impact neonatal herpes incidence.

Current neonatal herpes prevention strategies focus on pregnant women with recurrent symptomatic genital HSV and offer antiviral suppressive therapy in the last month of pregnancy to prevent lesions at the time of labor, and cesarean section for women with genital lesions at the time of labor. This approach has not resulted in a decrease in neonatal herpes incidence (7), probably because the risk of neonatal herpes in women with recurrent genital herpes is low. (5)

National seroprevalence data show that 78% of pregnant women are HSV-2 seronegative (8). We and others showed that about 5% of HSV-2 seronegative women have partners with HSV-2 who pose a potential risk of HSV transmission during pregnancy (9,10) ; among serodiscordant couples, 14-20% of women acquired HSV-2 during pregnancy. (10) Because most persons with genital herpes are unaware that they are infected and most often HSV acquisition is asymptomatic(11), identification of women at risk for HSV acquisition in pregnancy requires maternal HSV serotesting to identify HSV susceptible women, and, optimally, serologic testing of their sex partners to identify the women at highest risk of acquisition.

Routine HSV serotesting in pregnant women, and their partners, is controversial due to issues of effectiveness, cost, and patient acceptance.(12-14) Although acceptability studies (15,16) and clinical practice suggest that women would undergo HSV serotesting during pregnancy, no study addresses the feasibility of partner testing among pregnant women known to be susceptible to HSV-2. This study estimates test acceptance among couples in which the pregnant woman is known to be HSV-2 seronegative and identifies factors associated with testing.

Methods

Pregnant women were tested for HSV by Western Blot as part of routine prenatal care at the University of Washington.(17) Between July 2001 and August 2006, pregnant women receiving care at University of Washington prenatal clinics were approached for enrollment in an ongoing behavioral intervention study to prevent maternal HSV acquisition in pregnancy if the woman was willing to be approached regarding HSV studies, was HSV-2 seronegative, ≤ 31 weeks gestation, older than age 18, and English speaking (94% of eligible patients were approached). This study was approved by University of Washington Human Subjects Review Board, and all participants signed a consent form.

Study procedures included a baseline questionnaire regarding demographic and historical information, sexual history, information about current and past sexual partners, and current sexual behaviors. Women were given standardized counseling regarding safer sex practices to prevent acquisition of genital herpes during pregnancy based on their serologic status. This included a discussion with the HSV study coordinator, a copy of a 10 page booklet about herpes in general, a 2 page handout about herpes in pregnancy, and a laminated card specifying safer

sex techniques. To better define their risk of exposure to HSV during pregnancy and individualize safer sex practice recommendations, enrollees were asked to invite their sex partners for free serologic testing for HSV-1 and HSV-2 any time prior to delivery. Partner testing was encouraged but not required for study participation. The study coordinator spent approximately 5 minutes discussing why partner testing would be useful, suggested that the participant share the educational materials with her partner, and provided her with a copy of the consent form for the partner that again reviewed the risks of HSV transmission in pregnancy. Regardless of partner participation, women in the study completed daily paper-based diaries of sexual activity that were returned monthly to study personnel either by mail or in person at the time of routine prenatal visit. Women also completed additional sexual behavior questionnaires 1-2 times prior to delivery, and once immediately post-partum. Serologic results of the partner testing, and the effect of testing on sexual behavior in pregnancy will be published when the behavioral intervention trial concludes.

The following information about sex partners was collected from the female participant regardless of whether her sex partner presented for serologic testing: partner race/ethnicity, sexual frequency (oral and genital), sexually monogamous with partner, belief that partner was sexually monogamous, whether partner was considered a steady or casual partner, if the participant believed the partner had genital or oral herpes and if so, how often the partner had outbreaks and if sexual practices changed at the time of outbreak.

Only women who reported at least one sexual partner during pregnancy were included in analyses. Univariable and multivariable logistic regression compared maternal, partner, and relationship characteristics among participants whose partners had HSV serologic testing compared to those whose partners did not. Multivariable models of predictors of partner testing were developed by including all variables that were significantly associated with partner testing at the 0.2 level in univariable analysis, and then successively removing variables that were not statistically significant at the 0.05 level and did not influence covariate estimates by more than 20%. Thereafter, we checked for the influence and significance of other covariates that had not been included in the model originally. In the case of variables that described similar concepts, only one variable was chosen for the model. Among marital status, monogamy, and steady versus casual partner, marital status was used in multivariable models because it had the strongest univariate relationship with partner testing and only 3 enrollees reported their partnership as casual. Since most relationships were racially concordant (78%), we chose maternal race rather than partner race for multivariate models. White and Asian races were combined for the referent maternal race category since their estimates were very similar. Interaction terms were included to test for effect modification when feasible; sample size did not permit testing all possible interactions. Two-tailed p-values of 0.05 were considered statistically significant.

Results

During the study period, 94% of eligible prenatal patients were invited to participate and 335 (28% of those invited) HSV-2 seronegative pregnant women enrolled and completed the study. Reasons for refusal were: “not interested” (54%), “too busy” (20%), “not sexually active” (3%), “too personal/too embarrassing” (6%), and “other/unknown” (17%). Twenty women either had partners that were out of the state or country, or reported no sexual partner during their pregnancy and thus were excluded from statistical analyses.

The median age of the clinic population during the study period was 31 years, 50% were white, 10% African American, 10% Asian, 6% Hispanic, and 24% unknown race. Among 315 women included in the analysis, the median age was 30 years (range 15-51), 79% of participating women were white, 56% reported annual household income >\$50,000, and 93% were married

or living with their partners. All but 3 participants characterized their partner as their main or steady partner. All but one participant had only one partner during pregnancy; this participant had 3 partners during pregnancy, and none were tested for HSV. The median duration of relationship was 5.7 years, and 55% of participating women were HSV-1 seropositive.

Of the 315 women enrolled, 242 (77%) had partners who presented for HSV serologic testing. Partners of women who were married or living with their partner were more likely to be tested than partners of women who were separated, divorced, or not living with their partner (OR 5.05, 95% CI 2.03, 12.53). Partners of women who believed their partner had a history of oral herpes were more likely to be tested (OR 2.26, 95% CI 1.09, 4.67), as were partners who had a history of genital herpes (OR 2.83, 95% CI 0.35, 22.72), although neither comparison approaches statistical significance because relatively few of the women believed that their partner had oral (23%) or genital (3%) herpes. However, in the 10 couples in which the male partner was believed to have a history of genital herpes, 9 male partners were tested. Partners of African-American participants were less likely than partners of white or Asian participants to be tested (OR 0.21, 95% CI 0.06, 0.69) and partners of women with more than 2 person households were less likely than those with fewer person households to be tested (OR 0.52, 95% CI 0.31- 0.89). Remaining factors examined including maternal HSV serostatus, age, education, income, history of oral and genital herpes, and duration of relationship, were not significantly associated with partner testing. (Table 1) Notably, 22 of 29 (76%) of couples who reported duration of relationship <1 year underwent partner testing, consistent with the rate for entire study population.

In multivariable analysis, marital status, maternal education, race, age, and household size, remained important predictors of partner testing (Table 2). Marital status was the strongest predictor of partner testing with couples who were married or living as married substantially more likely to be tested than those who were not living together (aOR 7.72, 95% CI: 2.47, 24.15). Surprisingly, partners of women with a college degree were less likely to be tested than those less educated (aOR 0.43, 95% CI: 0.19, 0.98) in multivariable analyses, although this factor was not associated with partner testing in univariable analysis. African-American race remained strongly inversely associated with HSV partner testing (aOR 0.17, 95% CI: 0.04, 0.71).

Partner testing was more frequent among women who believed their partner had a history of oral herpes, although this association did not reach statistical significance (26% v. 14%, aOR 2.09, 95% CI 0.96, 4.58, $p=0.05$). To investigate if the effect of partner history of oral herpes varied by maternal HSV-1 serostatus we included an interaction term for these two variables in the multivariable model. Although the interaction term was not statistically significant ($p=0.38$) and therefore was removed from the final model, the odds ratio point estimates were of interest. Among HSV-1 seronegative women, 94% of partners with oral herpes were tested compared to 73% of partners without a history of oral herpes (aOR 5.99 95% CI: 0.72 –50.09, $p = 0.10$). In contrast, among HSV-1 seropositive women, 84% of partners with oral herpes and 74% of partners without a history of oral herpes were tested (aOR 1.49 95% CI: 0.60 –3.69, $p=0.39$).

DISCUSSION

This study of HSV serologic testing in pregnancy revealed several important insights regarding partner testing. Among partners of pregnant women, HSV testing occurred at a relatively high frequency regardless of duration of partnership, with partners in relationships of less than one year, a group at increased risk for maternal HSV acquisition(10), as likely to undergo testing as those in longer term relationships. Further, most couples in which the woman believed her partner had oral or genital herpes underwent partner testing, again suggesting that testing may

be feasible in these groups previously identified at higher risk for maternal acquisition of HSV during pregnancy (10). Partner testing was least likely to occur in African-American couples and further study of this disparity is warranted. Not surprisingly, women who were married or living as married were most likely to have their partners tested reflecting the commitment of the relationship, as well as the ready access to the partner, and unmarried women were least likely to have their partners tested.

The percentage of partners tested in this study was higher than we experienced in a prior study of HSV acquisition among serodiscordant couples in which about 50% of partners who were approached agreed to serologic testing. (10) The main differences between the two studies were the educational element of the current study, and, potentially, the patient population that enrolled. Enrollees in the current study agreed to complete sex histories, sex diaries, and were interested in education regarding neonatal herpes prevention. The prior study did not require sex diaries, did not provide enhanced neonatal herpes education, and only involved one or two visits with the study coordinator. As such, it is likely that the current study participants were motivated and knowledgeable about HSV prevention as a result of the behavioral intervention portion of the study suggesting that with increased education about neonatal herpes, women and their partners accept HSV testing.

Limitations of our study include generalizability to other patient populations. Although 94% of eligible women were approached for study enrollment, only 28% of those approached enrolled, consistent with other studies of behavioral interventions to prevent sexually transmitted diseases.(18) The women who participated in this study were interested in participating in HSV related research and were willing to complete sex diaries and enhanced HSV education. As such, they likely were motivated to undergo partner testing to determine their HSV risk status. The feasibility of partner testing in prenatal populations with greater ethnic and economic diversity requires investigation, as most of our study population was white and had relatively high socioeconomic status, consistent with the demographic distribution of women at our prenatal clinics. Further, all but 3 participants characterized their partner as their main, steady partner, and almost all were monogamous. Whether testing multiple partners during pregnancy is feasible could not be addressed in this study population. Thus, conducting similar investigations in other populations may be of interest.

Currently, guidelines for prevention of neonatal herpes focus on pregnant women who are known to have genital herpes. The American College of Obstetricians and Gynecologists supports suppressive antiviral prophylaxis for women with recurrent lesions during pregnancy, and cesarean delivery in the presence of active genital lesions at the time of labor. (19) Although these methods may be effective to prevent neonatal transmission in women with known genital herpes, they do not apply to women whose infants are at highest risk for neonatal HSV. Women who acquire herpes in late pregnancy and do not have lesions at the time of labor account for most cases of neonatal herpes. (5) One potential strategy to address this issue is to identify serodiscordant couples by HSV serologic testing in pregnancy, and provide interventions such as abstinence and counseling to reduce unprotected coital or oral-genital contact. (20) Recent studies in non-pregnant women suggest knowledge of HSV-2 status can reduce the risk of HSV-2 transmission,(21) and identification of HSV discordance in couples is increasingly promoted as a prevention strategy .(22) Further, identification of couples who are serodiscordant for HSV allows for increased education and opportunities for risk reduction by condom use (23) and, perhaps, anti-viral suppressive therapy in the male source partner (24) to prevent maternal acquisition during pregnancy.

Our study suggests that partner testing among HSV-2 seronegative pregnant women may be feasible and provides an estimate of the percentage of partners willing to undergo testing. If this approach results in a reduction of sexual exposure to HSV, it may provide a prevention

strategy that is needed for women that both are at highest risk and account for the majority of neonatal HSV cases.

Whether serologic testing of pregnant women and their partners is cost-effective to prevent neonatal herpes is debated. The published cost-effectiveness analyses report widely discrepant results, in part because estimates of outcomes are imprecise. In addition, including HSV-1 testing increases cost of testing substantially. (12-14) Unfortunately, HSV-1 cannot be ignored because it may be an increasingly common cause of genital herpes,(25-27) and is responsible for almost half of the neonatal herpes cases described at our institution as well as in a nationwide surveillance study in Canada.(5,28) Our study focused on HSV-2 seronegative women. Women who are HSV-2 seropositive do not appear to be at risk for genital HSV-1 acquisition. (5) However, HSV seronegative women with partners who have HSV-1 are at risk for HSV-1 genital acquisition either from genital to genital contact if their partner has genital HSV-1 or oral-genital contact if their partner has orolabial HSV-1. If the site of infection is unknown, prevention through safer sex practices might be difficult. Thus, the effect of HSV-1 testing requires study, in addition to further study of the cost effectiveness of testing in pregnancy.

In this population of women interested in neonatal herpes prevention, partner testing for HSV-1 and HSV-2 occurred at high frequency. Despite the inherent limitations of the design of this study, the data suggest that it may be feasible to identify serodiscordant couples by serologic testing during pregnancy. Further study of the acceptance of testing in more diverse populations is warranted. Whether testing altered sexual behavior in HSV serodiscordant couples to reduce the morbidity of HSV in such high risk women is currently under investigation.

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Table 1

Maternal and partner characteristics of study participants and univariate odds ratios [OR] for partner testing*

Maternal Characteristics	Total (n=315) N (%)	Partner Tested (n=242) N (%)	Partner Not Tested (n=73) N (%)	Univariate OR (95% CI)	P-value
Age: 18-26 years	86 (27)	61 (25)	25 (34)	1.00	0.14
26-30 years	75 (24)	63 (26)	12 (16)	2.15 (0.99, 4.66)	
30-35 years	93 (30)	68 (28)	25 (34)	1.11 (0.58, 2.14)	
35-51 years	61 (19)	50 (21)	11 (15)	1.86 (0.84, 4.15)	
Race/Ethnicity					
White or Asian	276 (87)	213 (88)	63 (86)	1.00	0.009
African American	12 (4)	5 (2)	7 (10)	0.21 (0.06, 0.69)	
Hispanic/Other	27 (9)	24 (10)	3 (4)	2.37 (0.69, 8.12)	
Parity					
0	258 (82)	201 (83)	57 (78)	1.0	0.34
≥1	57 (18)	41 (17)	16 (22)	0.73 (0.38-1.39)	
Level of Education					
≤ Some college	114 (36)	89 (37)	25 (34)	1.00	0.69
College graduate	201 (64)	153 (63)	48 (66)	0.90 (0.52, 1.55)	
Household income					
< \$30,000/year	76 (24)	53 (22)	23 (32)	1.00	0.25
\$30,000 --\$50,000	57 (18)	44 (18)	13 (18)	1.47 (0.67, 3.23)	
> \$50,000/year	176 (56)	140 (58)	36 (49)	1.69 (0.92, 3.11)	
>2 people in household	142 (45)	100 (41)	42 (58)	0.52 (0.31, 0.89)	0.02
HSV-1 seropositive	172 (55)	134 (55)	38 (52)	1.14 (0.68, 1.93)	0.62
History of Oral Herpes	68 (22)	53 (22)	15 (21)	1.11 (0.58, 2.11)	0.76
History of Genital Herpes	9 (3)	6 (2)	3 (4)	0.59 (0.14, 2.43)	0.48
Marital Status					
	21 (7)	9 (4)	12 (16)	1.00	<0.001

Maternal Characteristics	Total (n=315) N (%)	Partner Tested (n=242) N (%)	Partner Not Tested (n=73) N (%)	Univariate OR (95% CI)	p-value
Separated/Divorce/ Living separately	292 (93)	231 (95)	61 (84)	5.05 (2.03, 12.53)	
Married/living together					
Monogamous, self-report,	290 (92)	222 (92)	68 (93)	1.02 (0.36, 2.89)	0.97
Partner Considered "Steady"	308 (98)	237 (98)	71 (97)	6.68 (0.60, 74.71)	0.11
Duration of Relationship					
9 yr	86 (27)	68 (29)	18 (25)	1.0	0.91
5-9 yr	88(28)	65 (27)	23 (32)	0.75 (0.37,1.51)	
3-5 yr	58(18)	46 (19)	12 (17)	1.01 (0.45,2.31)	
1-3 yr	48(15)	36 (15)	12 (17)	0.79 (0.34,1.83)	
≤ 1 yr	29(9)	22 (9)	7 (10)	0.83 (0.31,2.25)	
Partner Characteristics					
Race/Ethnicity					
White or Asian	268 (85)	207 (86)	61 (84)	1.00	0.32
African American	22 (7)	14 (6)	8 (11)	0.52 (0.21, 1.29)	
Hispanic/Other	22 (7)	18 (7)	4 (5)	1.33 (0.43, 4.07)	
Monogamous per enrollee	283 (90)	220 (91)	63 (86)	2.05 (0.90, 4.71)	0.10
Oral Herpes per enrollee	72(23)	62 (26)	10 (14)	2.26 (1.09, 4.67)	0.02
Genital Herpes per enrollee	10 (3)	9 (4)	1 (1)	2.83 (0.35, 22.72)	0.26

* numbers may not add to totals due to missing data, which comprises < 3% of total participants

** OR is for the effect of each 5 additional years

Table 2

Multivariate Model for Odds of HSV Partner Testing (N=306)

Variable	Adjusted OR (95% CI)	p-value
Maternal Age*:		
Among those with 1-2 household members:		0.02
18-26 years	1.00	
26-30 years	2.92 (1.17, 7.29)	
30-35 years	2.71 (0.97, 7.59)	
35-51 years	5.68 (1.69, 19.10)	
Among those with >2 household members:		0.009
18-26 years	1.00	
26-30 years	2.92 (1.17, 7.29)	
30-35 years	0.52 (0.18, 1.54)	
35-51 years	1.10 (0.34, 3.49)	
Maternal Race:		0.01
White or Asian	1.00	
African American	0.17 (0.04, 0.71)	
Hispanic or Other	2.60 (0.66, 10.22)	
Maternal Education:		
some college or less	1.00	0.04
college degree or more	0.43 (0.19, 0.98)	
Number in Household*: >2 vs. ≤ 2		
among those under 30 years old	1.00 (0.43, 2.35)	0.99
among those over 30 year old	0.19 (0.08, 0.46)	<0.001
Marital Status:		
separated/divorced/not living with partner	1.00	<0.001
married or living with partner	7.72 (2.47, 24.15)	
Perceived partner history of oral herpes:		
no	1.00	0.05
yes	2.09 (0.96, 4.58)	

* Since this model includes an interaction between maternal age over 30 and number in household, the estimates for these two variables were provided within each stratum of the other variable. Each variable was adjusted for all other variables in the table.