ORIGINAL INVESTIGATION

Persistent Stress as a Predictor of Genital Herpes Recurrence

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Background: Results of several studies suggest that psychological stress and negative mood can trigger genital herpes recurrences, but results are inconsistent.

Objective: To determine whether short-term or persistent psychological stress or specific negative moods are predictive of genital herpes recurrences in women.

Methods: A prospective cohort study followed up participants for 6 months using weekly assessments of stress and mood, monthly assessments of life change events, and diary reports of genital herpes recurrences confirmed by medical examination when feasible. The community sample consisted of 58 women, aged 20 to 44 years, with a 1- to 10-year history of visible genital herpes recurrence and at least 1 recurrence in the previous 6 months.

Results: Persistent stress predicted recurrence in the subsequent week (odds ratio, 1.08 per unit increase in stress; 95% confidence interval, 1.01-1.15; $P = .03$). After adjusting for recurrence in the previous week, the more weekly persistent stress reported, the greater the likelihood of recurrence the following week. Also, an increased recurrence rate occurred after the month during which participants experienced their highest levels of anxiety ($P = .03$). There were no significant associations between recurrence and short-term stress, life events, depressive mood, anger, or phase of menstrual cycle.

Conclusions: Persistent stressors and highest level of anxiety predicted genital herpes recurrence, whereas transient mood states, short-term stressors, and life change events did not. Women with herpes can be reassured that short-term stressful life experiences and dysphoric mood states do not put them at risk for increased outbreaks of recurrent genital herpes.

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RESULTS OF clinical studies have long suggested a link between stressful life experiences and the recurrence of oral or genital herpes simplex virus (HSV) lesions. Results of recent animal studies[1] using the mouse footpad infection model with HSV-1 demonstrate that restraint stress can alter HSV pathogenesis via specific immunologic mechanisms. Although many patients believe that stress may trigger recurrences,[2,3] the empirical research base linking stress and genital herpes recurrences in humans is weak. A few studies[4-6] report statistically significant relations between genital HSV recurrences and stressful life experience or "perceived" stress, but most[7-12] do not. However, neither the characteristics of stressors, eg, their type, intensity, or duration, nor their effect on certain subgroups of vulnerable individuals have been considered in these studies.

In addition to stress, negative mood has also been investigated as a potential trigger of recurrences. Symptoms and signs of psychiatric dysfunction have been linked to higher genital herpes recurrence rates[7,11,13,14]; however, the evidence[4,7,12,15] relating recurrence and personality trait measures of negative mood is inconsistent. Only a few studies[9,16,17] have examined whether elevation in specific mood states (eg, anxiety and depressive mood) is associated with rates of genital HSV recurrence.

The inconsistencies in the findings relating stress and mood to genital HSV recurrence may be caused by several methodological shortcomings of these studies. First, stress and mood are often assessed retrospectively after recurrences have occurred, and therefore, stress reporting may be confounded by the recognition of recurrence or by mood states induced by having a recurrence. Furthermore, when recurrences are assessed ret-

PARTICIPANTS AND METHODS

PARTICIPANTS

Our sample of 58 women, aged 20 to 44 years (mean ± SD, 31.8 ± 5.8 years), had a history of visible genital herpes (documented by culture) for 1 to 10 years (mean ± SD, 5.1 ± 3.3 years) and at least 1 recurrence in the 6 months before starting the study (mean ± SD, 4.1 ± 2.8; range, 1.0-15.0). We chose these inclusion criteria to focus our study on patients with regular recurrences, and to avoid confounding caused by disease history variables (eg, viral shedding may be more frequent in the first year after initial infection[18]). We restricted our sample to women with visible genital herpes lesions in order to reduce the possibility of participants' underreporting of internal lesions. Furthermore, because we believed that men and women might differ in how they experienced or reported negative moods and stressors, and could show different relations between stressors and recurrence, we limited our study to women.

All participants had cultures taken at least once by the referring physician or study physician to document having HSV type 2. Only women who reported previous visible HSV lesions were accepted into the study. Lesions were located in the outer vaginal area (25 participants [43%]), inside the vagina (2 [4%]), in a nonvaginal site (eg, anus, buttocks, and coccyx) (6 [10%]), or in a combination of vaginal and nonvaginal sites (25 [43%]). The 56 white and 2 African American participants had a mean ± SD of 16.4 ± 1.7 years of education. They were recruited from newspaper advertisments and flyers posted on bulletin boards at nearby San Francisco, Calif, colleges and medical centers, and were paid $60 or $125 for participation ($125 for those also participating in a substudy requiring blood draws). Individuals were excluded for any medical condition, medication use, or treatment that could affect their immune system or recurrence directly: use of oral acyclovir, use of adrenal corticosteroids or estrogen replacement therapy, use of antidepressive medication, cigarette smoking, pregnancy, breastfeeding, anorexia, recent surgery, severe allergies, other current sexually transmitted diseases, immunodeficiency disease, neoplastic diseases, autoimmune diseases, rheumatic fever, diabetes, seizures, endocrine disorders, chronic infection during the past year (such as hepatitis or mononucleosis), recent malaria or anemia, radiation therapy, or chemotherapy. Patients were excluded if any of these were present during the 6-month study. We also excluded individuals whose native language was not English and those who were legally blind.

Of 71 women recruited, 58 completed the study and 13 did not. One of the 13 women did not maintain exclusions, and 12 chose to terminate their participation. Reasons for termination included moving (n = 1), husband's disapproval (n = 1), being uncomfortable with the blood draws (n = 2) (a subgroup of patients also had blood drawn monthly, and the results will be reported in a separate article), and finding the study too time-consuming and inconvenient (n = 8). To determine whether dropouts differed from participants, we compared baseline measures between the 2 groups using 2-sample *t* tests. Results showed that dropouts were significantly younger than participants (mean age, 27.9 vs 31.8 years; $P = .03$). There were no significant differences between dropouts and participants regarding years of education ($P = .17$); number of herpes recurrences in the 6 months before study entry ($P = .26$); week 1 scores for short-term stress ($P = .09$), persistent stress ($P = .18$), anxiety ($P = .48$), or depressive mood ($P = .72$). Thus, the final sample was not selectively biased on socioeconomic status, recurrence frequency, or key psychological variables.

PROCEDURE

The study protocol was approved by the institutional review board at the University of California, San Francisco. All participants gave written informed consent, filled out personality questionnaires, and provided a health history. Participants were interviewed and filled out a life events questionnaire—the Life Experiences Survey—monthly; at the end of each week, they completed and mailed in a Weekly Stress Log, Weekly Health Form, and Mood Questionnaire.

At times of prodromal symptoms (eg, burning or itching) or visible herpes recurrence, participants filled out a daily calendar to document the length and symptoms of the episode. Participants were also instructed to go to participating physicians or nurse practitioners for clinical documentation of suspected HSV outbreaks. In many cases, this proved to be impractical because of weekends, vacations, and scheduling time conflicts; thus, only 49% of recurrences were medically examined. In 91% of cases, results of the examination verified the recurrence as herpes. Unverified cases were not dropped from the sample because we could not confirm that they were false positives (the examining physicians could neither confirm that the lesions were herpes nor provide an alternate diagnosis). Some examinations were performed during the healing phase of the recurrence, making confirmation more difficult.

PSYCHOLOGICAL MEASURES

Stress Measures

Two different stress measures were used: the Life Experiences Survey and the Weekly Stress Log. A modified version of Sarason's Revised Life Experiences Survey[19,20] was administered monthly to assess major life change events. The participant indicated which of 57 life change events (such as marital separation or being fired from a job) had occurred during the past month (multiple occurrences of the same event were noted), whether the event was good or bad, and how great an effect the event had on her life on a 7-point scale (1 indicates not at all; 7, extremely). "Effect ratings" of negative events (those rated "bad") were summed for each month to obtain a weighted score; we also obtained a monthly count of negative events. Sarason et al[19] support the construct validity of this measure.

The Weekly Stress Log was used to differentiate short-term and persistent stressors, and to avoid problems in recall.[21] A detailed description is provided in a recent article.[22] The Weekly Stress Log measures show adequate construct validity, with moderate correlations between life change event scores, and short-term ($r = 0.33$) and

Continued on next page

persistent ($r = 0.46$) stress. Short-term and persistent stress ratings are not significantly correlated with each other or with personality trait measures of dispositional optimism or negative affectivity.[22] On the log, participants were asked to provide brief descriptions of stressors that had occurred during the past week, rate their subjective stressfulness on a 7-point scale, and specify how long each situation had been stressful. Up to 10 situations could be listed. Stress situations were later coded as to their duration (short term or persistent) using information from the current and previous stress logs. Situations reported as stressful for 7 days or less were coded as short term. Situations reported as being stressful on the current week's log and for at least 7 days duration on the previous week's log (thereby indicating a duration of >7 days) were considered persistent during the second week and for any immediate subsequent weeks that they were listed on the weekly log. The greater-than-1-week period was chosen because we wanted to distinguish relatively short-term stressors from those that would require more sustained coping efforts. To obtain weekly short-term and persistent stressor scores, we summed the appraised stress ratings for the situations coded that week in each duration category. For short-term and persistent stressors, the weekly potential range of values is 0 to 70 (0-10 situations could be reported with a 1-7 stress rating per situation listed). We used stress ratings because we were interested in the predictive power of a person's appraisal of the stressfulness of current stressors.[23]

Mood Measures

A modified version of the Mood Questionnaire[24] was used weekly to assess negative mood on 3 dimensions—depression, anger, and anxiety. Although Ryman et al[24] label the subscale as fear, we refer to it as anxiety because its 6 items (afraid, alarmed, uneasy, hopeless, insecure, and jittery) overlap with items on other commonly used anxiety scales. We changed the response format from a 3-point to a 5-point scale (1 indicates not at all; 2, a little bit; 3, moderately; 4, quite a bit; and 5, extremely), following the work of Hall et al.[25] The Mood Questionnaire shows a clear factor structure, moderate test-retest correlations (indicating the scale taps transitory mood states), adequate evidence of construct validity, and good predictive validity.[24,26]

Personality Trait Measures

We used the short 20-item form[27] of the Taylor Manifest Anxiety Scale as a measure of negative affectivity, or trait mood— the disposition to experience negative affect in a variety of situations. The short form correlates 0.91 with the full Taylor Manifest Anxiety Scale; the internal consistency reliability is 0.76. Watson and Clark[28] present support for the construct validity of this measure.

The 12-item Life Orientation Test of Scheier and Carver[29,30] was used to measure dispositional optimism, a personality trait based on individuals' expectancies for the occurrence of good vs bad future outcomes. Optimists expect future successes; pessimists anticipate poor outcomes. We changed the Life Orientation Test 0 to 4 response format to a 1 to 5 scale so that all the questionnaire items in our study had "1" as the lowest rating. The test-retest reliability (0.79 for a 4-week interval) and discriminant and convergent validity are adequate.[29,31]

OTHER MEASURES

Weekly Health Form

The weekly health form contains questions about alcohol consumption, cigarette use, medications taken, illnesses and symptoms of illness, other health variables, date of menstrual period, and whether a recurrence or prodrome began that week. The form was used to pinpoint the weeks when an infection had occurred, to check on completion of the Herpes Recurrence Form and the maintenance of exclusion criteria and other restrictions, and to evaluate the sleep adequacy and alcohol consumption of participants. Infections were considered to be present if, on the illness checklist, participants reported colds, upper respiratory tract infections, fever, or stomach flu, or wrote in an infectious illness (eg, sepsis) under "skin infection" or "other illness." Local infections (such as infected fingers) were not included.

Recurrences

At times of prodromal symptoms (eg, burning or itching) or visible recurrence, participants completed the Herpes Recurrence Form (which charted a daily calendar of recurrence stages). Thus, we could calculate how many recurrences (defined as the presence of visible redness, bumps, or lesions) the participant had during the study, and when each recurrence began. Participants were also instructed to go to participating physicians or nurse practitioners for physical examination of their lesions. During the examination, cultures were also taken for participants without previous culture reports indicating HSV-2 typing. As noted earlier, not all participants could make timely appointments because of weekends, vacations, and scheduling conflicts; only 49% of recurrences were physically documented.

STATISTICAL ANALYSES

We used 2 different analytic strategies to investigate whether the likelihood of subsequent recurrence varied as a function of stress or mood. First, we examined whether the likelihood of recurrence was affected by level of stress or negative mood states in the previous week (autoregressive logistic model). Second, we investigated whether recurrence rate changed after extreme changes in stress or negative mood levels (paired t test analyses), that is, following the months with the highest compared with the lowest levels of stress (or negative moods).

We assessed the associations of weekly stressor and mood variables with likelihood of recurrence (yes/no) in the following week using an autoregressive logistic model,[32] which included stress (or mood) variables and recurrence in the previous period as the covariates that varied over time. The autoregressive logistic model is a binary analog of the autoregressive models used to analyze continuous response data (see, eg, Ware[33]). We assumed a first-order autoregressive model for the recurrences; that is, we allowed the probability of a recurrence in a given period to depend on whether the participant had a recurrence in the preceding period. If a participant had a

recurrence that carried over until the next period, we considered the recurrence outcome for the second period to be missing. However, we used the recurrence information in the second period as a covariate to predict future recurrence. We used the SAS LOGIST[34] program to fit the autoregressive logistic models; there were 23 prediction weeks in this analysis. We fit separate models for each stress or mood variable, and evaluated whether personality trait measures related to negative affectivity or optimism moderated the relation between stress and recurrence.

To investigate whether recurrence rate changed only after extreme changes in stress or mood levels, we compared the recurrence rate in the 4 weeks after the month participants reported the highest short-term stress (we also repeated the analysis for each negative mood) with the rate for the 4 weeks after the participants' lowest short-term stress (or negative mood) months. (We could not do these analyses for persistent stress or our major life change events measure because, for most participants, there was too little variability by months for these analyses to be meaningful.) From our 4-week averages, we identified the highest and lowest short-term stress (or mood) months for each person. One participant was dropped from the anger and anxiety analyses because of a lack of variability in her monthly aggregated mood reports. We carried out a paired *t* test to compare across participants the number of recurrences after high vs low short-term stress (or mood) months. In all analyses, we used $P = .05$ as the criterion for statistical significance.

To examine whether recurrence rate was related to menstrual cycle, we used a repeated-measures analysis of variance. We divided the cycle into 5 phases: menstrual (days 1-5), postmenstrual and preovulatory (days 6-10), ovulatory (days 11-17), postovulatory (days 18-21 or longer depending on the length of the cycle), and premenstrual (7 days before the first day of the next menstrual cycle). Each recurrence was coded according to its phase in the woman's cycle, and the number of recurrences each participant had in each phase was divided by the length of the phase (eg, 5 days for menstrual phase and 7 days for premenstrual phase).

rospectively, the accuracy of the patient's report may be limited by memory, especially when asked to report on recurrences that occurred months earlier. Second, in most previous studies, presence of a herpes recurrence is based on self-report and is not confirmed by physician examination. Reports of recurrences could be confounded by mood state, thereby inflating the relation between mood and outcome. Third, most study designs use summary assessments of stress or mood over extended periods (eg, 1 month or 1 year). These designs do not permit analyses of the rapid relation between stress and the onset of a recurrence that patients frequently describe. Fourth, many studies rely only on life event scales to measure stress, which do not capture the broad range of life difficulties (eg, ongoing stressors and disappointments over events that did not happen) that could potentially trigger recurrences.

Table 1. Means ± SDs and Ranges for Psychological and Recurrence Variables*

Variable	Mean ± SD (Range)
Psychological factors	
Short-term stress	10.62 ± 5.97 (1.40-31.39)
Persistent stress	0.81 ± 0.96 (0-5.16)
Life change events, count	1.07 ± 0.83 (0-4.17)
Life change events, weighted	4.56 ± 3.69 (0-16.83)
Depressive mood	11.21 ± 3.28 (6.08-21.27)
Anger	11.04 ± 3.34 (6.04-20.20)
Anxiety	10.38 ± 3.52 (6.12-19.32)
Optimism	30.28 ± 5.40 (14.00-40.00)
Negative affectivity	8.17 ± 4.88 (1.00-19.00)
HSV recurrence outcome	
Recurrences during 6-mo study	2.95 ± 1.87 (0-7.00)
HSV disease history	
Years with genital herpes, No.	5.09 ± 3.26 (1.00-10.00)
Recurrences in 6 mo before starting study, No.	4.07 ± 2.78 (1.00-15.00)

**Short-term and persistent stressors and moods were assessed weekly; life change events were assessed monthly. For the descriptive purposes of this table, stressor and mood measures were averaged for the 24 weeks of data. Weekly means are listed for the stress and mood variables measured weekly, and monthly averages for the life change measures assessed monthly. For mood variables, the potential range of values is 6-30 (6 items per scale, with a 1-5 rating per item). HSV indicates herpes simplex virus.*

Other methodological weaknesses include small sample sizes and inadequate or variable follow-up.

The purpose of this study was to examine whether persistent or short-term stress triggers recurrences of genital herpes. In addition, we examined life change events and different mood states as predictors of recurrence. The study was prospective and minimized retrospective bias and memory limitations by using weekly assessments of persistent and short-term stressors and mood, daily diary reports of HSV recurrences, and documentation of these recurrences by physicians or nurse practitioners when feasible. A statistical model used data from 24 weeks to determine whether weekly increases in stress and mood predict subsequent recurrences in the following week.

RESULTS

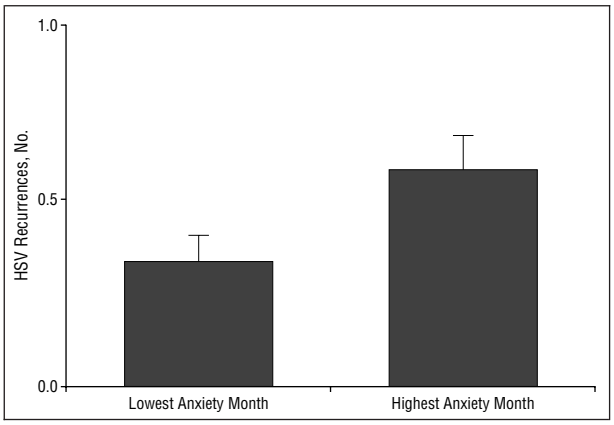
To characterize the sample as a whole, **Table 1** presents the mean ± SDs and ranges for the psychological and recurrence variables measured in this study. Participants experienced frequent HSV recurrences (average of 3 during the 6-month study). Study participants also experienced relatively low average levels of stress and negative mood, but there was considerable variation across participants. For example, for short-term stress, average weekly scores ranged from 1.40 to 31.39; persistent stressors were less frequent, and there was a narrower range (average weekly scores ranged from 0-5.16).

The types of stressors reported on the Weekly Stress Log were wide ranging. Examples of short-term stressors reported included "had to fly on an airplane which is stressful" (3 hours), "car was vandalized" (1 day), and "cat breaking her leg" (7 days). Examples of persistent stressors reported included "worried about my sister who is pregnant and alone" (3 weeks), "ongoing uncertain-

Table 2. Association of Stress and Mood Variables (in Previous Week) With Recurrence (in Subsequent Week)

Variable	Odds Ratio (95% Confidence Interval)	P*
Short-term stress	1.00 (0.98-1.02)	.67
Persistent stress	1.08 (1.01-1.15)	.03
Depressive mood	1.02 (0.99-1.06)	.15
Anger	1.01 (0.98-1.05)	.49
Anxiety	1.03 (0.99-1.07)	.11

**From the Wald statistic* $\hat{\beta}^2/\widehat{var}(\hat{\beta})$.



Mean rate of herpes simplex virus (HSV) recurrences in the month after the highest and lowest monthly levels of anxiety. Error bars indicate SEs.

ties about job prospect" (4 weeks), and "financial difficulties" (7 weeks).

Before carrying out the logistic model, we explored whether recurrences were associated with self-reported infections since we raised that question in a previous study.[9] Using the conditional likelihood approach for matched binary responses,[35] we examined whether the rate of recurrence was higher the week of or the week after a reported infection compared with noninfection weeks. Results revealed that the rate of recurrence was not associated with the week of an infection ($P = .55$). Odds ratio (OR) measuring the association of indicators for infection and recurrence in the same week was 0.85 (95% confidence interval [CI], 0.51-1.44). However, there was a significant negative relation between previous week of infection and recurrence ($P = .02$). The OR measuring the association between infection in the previous week and recurrence was 0.48 (95% CI, 0.26-0.88). Recurrences were less likely to occur the week after a reported infection.

Our first major analyses used an autoregressive logistic model to examine how weekly stressor and mood levels were associated with likelihood of a herpes recurrence in the subsequent week. Results showed that the only stress or mood variable significantly predictive of recurrence was persistent stress. After adjusting for recurrence status in the previous week, we found that the more persistent stress reported in a particular week, the greater the likelihood of a recurrence the following week (OR, 1.08 per unit increase in stress; 95% CI, 1.01-1.15; $P = .03$). By definition, to be classified as persistent, the same stressor had to persist for longer than 1 week. There were no significant associations for short-term stressors, depressive mood, anger, or anxiety. Additional adjustment for infection status in the previous week yielded nearly identical OR estimates and associated 95% CIs. **Table 2** presents the ORs (and 95% CIs) for the relation of each stress or mood variable and recurrence singly. We repeated the analyses, including personality-stressor interaction terms (for negative affectivity, then for optimism) in the model, to determine whether trait mood or optimism moderated the relation between stressors and recurrence. Results revealed no significant interactions ($P = .29$-$.88$ for the interaction coefficients). Furthermore, we examined the relation between stressful life change event values (assessed monthly) and likelihood of recurrence in the subsequent month, and found that neither the weighted negative life event score nor the negative life event count was significantly related to recurrence.

We also examined alcohol use and sleep insufficiency to determine whether these health variables were directly associated with recurrence outcomes or whether they moderated the relation between stress and recurrence. No participants in this sample consumed alcohol excessively (ie, averaged >2 drinks per day). Correlations indicated no significant relations between number of alcoholic drinks per week ($P = .24$) or nights of insufficient sleep ($P = .26$) and number of recurrences. Furthermore, alcohol use and sleep were not significant moderators of the stress-recurrence relation ($P = .39$-$.70$). In addition, analyses showed no relation between age ($P = .81$) or socioeconomic status (measured by years of education; $P = .90$) and number of HSV recurrences.

Our second set of analyses investigated whether recurrence rate would change only after extremely high stress or mood levels, that is, after months with the highest levels of short-term stress (or negative moods) during the 6 months. To investigate this question, we compared the recurrence rate in the 4 weeks after the month participants reported the highest short-term stress (or negative mood) with the rate for the 4 weeks after the participants' lowest short-term stress (or negative mood) months. Results showed that the only significant differences were found for anxiety. Participants had significantly more recurrences ($t_{56} = 2.30$; $P = .03$) after their highest anxiety month (mean, 0.57) than after their lowest such month (mean, 0.33): a 70% increase (**Figure**). There were no significant relations for short-term stress ($P = .64$), depressive mood ($P = .29$), or anger ($P = .93$).

Because some participants believed that their recurrences might be related to the menstrual cycle, we examined whether recurrence rates differed across participants during different menstrual phases. Data from 5 participants were withdrawn from this analysis because of incomplete information, no recurrences, or no menstrual periods. A repeated-measures analysis of variance revealed no significant differences in the number of recurrences experienced in each menstrual phase ($F_{4,52} = 1.17$; $P = .32$).

COMMENT

This study followed up 58 women with recurrent genital herpes for 6 months and determined whether weekly short-term and persistent stress levels and negative mood states or major stressful life events predicted subsequent HSV recurrences. Persistent stress was defined as the stressfulness of events that persisted for longer than 1 week; short-term stress ratings reflected events continuing for 1 week or less. Our results showed that persistent but not short-term stress predicted HSV recurrences. Higher levels of persistent stress resulted in an increase in the probability of recurrence. After adjusting for the past week's recurrence, for a 1-point increase in persistent stress, the odds of having a recurrence in the following week were 1.08 times greater for participants with higher persistent stress. If we recalculate the OR for a 3-point increase in persistent stress (eg, from 1, "not at all," to 4, "moderately," on our 7-point scale), the OR would be 1.26, indicating a 26% increase in the chance of a recurrence the following week for the person with the higher score. In other words, the occurrence of 1 moderately stressful experience lasting more than 7 days would increase by 26% the chance of having a recurrence in the following week.

In contrast to our findings with persistent stress, major life events did not predict recurrence, consistent with results of other studies[7-9,11,12] (compare Taylor[6]) that found no straightforward relation between life change events and genital herpes recurrence. This lack of relation may be partially caused by the low base rate of such major life events (mean, 1.07 negative life events per month in our sample). Short-term stress was common in our sample and did not predict recurrences, consistent with results of earlier studies[8-10] showing that monthly or weekly stress assessments were not linked to increased recurrence outcomes. Our findings suggest that stress might have been overemphasized as a potential trigger of herpes recurrences. Although results of animal studies show a strong stress effect on HSV susceptibility, the stressors used in animal research are usually long-term or extreme physical stressors. Our results indicate that a stressor might have to persist for it to trigger a herpes recurrence. Previous studies in humans were not designed to differentiate short-term from longer-term stressors, and might have obscured a relation with more persistent stressors.

It has been hypothesized that both neural (inciting viral replication in the sacral ganglion) and local (causing local immunologic controls to fail to protect host cells from viral invasion) mechanisms may be necessary for recrudescence to occur.[36,37] Thus, the link between persistent stress and recurrence may be partially mediated by the immune system because long-term stress has been associated with decreased natural killer-cell activity and impairments in cell-mediated responses in humans,[38,39] and immunologic processes may control viral replication or destruction of virus at the local site.[37] Furthermore, in the footpad animal model,[40] restraint stress decreased levels of HSV-specific cytotoxic T-cell activity and natural killer-cell activity, in addition to HSV pathogenesis. Nonimmunologic mechanisms involving the central nervous system could also be triggered by prolonged stressors through other pathways yet to be determined.

We found that increased levels of negative mood (anxiety, depressive mood, and anger) did not predict the timing of recurrences. However, peak levels of anxiety within persons (the highest monthly level of anxiety during the 6 months) were more likely to be followed by a recurrence. Our positive findings for peak anxiety are consistent with those of 2 prospective studies[16,17] that found significantly higher anxiety, but not dysphoria, before genital herpes recurrence. Within-person analyses may be a better test of the effects of mood on recurrence; because participants are compared with themselves, this eliminates concerns about preexisting differences between people. What seems to be most predictive of recurrence is the highest anxiety level for that person. In contrast, our results show that short-lived and moderate levels of negative mood do not put participants at increased risk for recurrence. It may be that only when anxiety exceeds a certain threshold for the individual can it increase the likelihood of a pathophysiological response.

Menstrual cycle results are consistent with those of 5 previous studies (compare Guinan et al[41]), which found no increases in genital herpes recurrences[7,16,42,43] or in asymptomatic genital herpes viral shedding[44] during any phase of the menstrual cycle.

Strengths of this study include its prospective design; weekly measurement of stress and mood; careful documentation of genital herpes history; detailed diary report of onset of recurrences, verified by clinical examination when feasible (in almost 50% of cases); careful screening of participants, including exclusion of those taking acyclovir; delineation of short-term and persistent stressors; investigation of personality factors as potential moderators; use of powerful statistical models that incorporate time ordering of the data; including within-person analyses; and a 6-month study period. A limitation of the study is its focus on women aged 20 to 44 years. Results might not generalize to men, women older than 44 years, women with internal (rather than external) lesions, nonvolunteer samples, or populations that are not primarily white or English speaking. Results also might not generalize to patients with oral herpes recurrences.[45]

In conclusion, the results of our study suggest that transient mood states or short-term stressors do not put women at risk for increased genital herpes recurrence. In our sample, persisting stressors or high prolonged levels of anxiety were required before an increased risk of recurrence was detected. Thus, women with herpes should be reassured that routine or brief stressful life experiences or dysphoric mood states might not put them at risk for increased outbreaks of recurrent genital herpes. Referral to counseling could be recommended for women experiencing persistent stressors or continuing high levels of anxiety; counseling and stress management could be used in conjunction with medications that suppress recurrent herpes.

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