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Depressed Mood and Herpes Simplex Virus-2 Immunoglobulin-G Levels in Pregnancy

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Abstract

Objective—Depressed mood is common in pregnancy, is associated with stress, and could result in immune suppression that may lead to latent herpes viral reactivation. This study investigated whether depressed mood is associated with higher herpes viral IgG levels in pregnant women.

Methods—Complete cross-sectional data from 247 pregnant women were available for this sub-study. The data included demographics, scores on the Perceived Stress Scale (PSS) and Profile of Mood States (POMS), and a panel of serum IgG levels for human herpesviruses.

Results—Only HSV-2 (genital herpes) IgG level was associated with PSS and POMS-Depression/Dejection (POMS-D) score. Hierarchical multiple regression analysis was used to examine the association of POMS-D with herpesviral IgG levels adjusting for demographic variables. In the final model AA race ($\beta = .251, p < .001$), older age ($\beta = .199, p = .002$), single marital status ($\beta = -.304, p < .001$), and depressed mood ($\beta = .122, p = .04$) were associated with HSV-2 IgG levels. In logistic regression, the strongest correlates of HSV IgG positivity were single marital status, followed by POMS-D scores and African American race.

Conclusion—Genital herpes is a concern in pregnancy. Antibody titers may indicate asymptomatic viral shedding, viral reactivation, or primary viral infection. Antibody levels may be higher due to the immune changes of pregnancy and to potential immune effects of depressed mood causing reactivation of latent HSV-2.

Keywords

Pregnancy; HSV-2; EBV; CMV; PSS; POMS-D; African American

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Conflict of Interest Statement:

All authors declare that there are no conflicts of interest.

INTRODUCTION

Pregnancy is a vulnerable time for women. Biobehavioral mechanisms interact to increase risks for stress, depressed mood and infection. This includes reactivation of latent viruses such as those of the Herpes family. Changes in hormone levels and the activity of the immune system participate in avoiding rejection of the fetus but may increase risks for certain infections. Soluble factors from trophoblastic cells inhibit maternal T cell proliferation and decrease natural killer (NK) cytotoxicity and interferon- γ (IFN- γ) [1, 2]. There is a general suppression of type 1 (cellular) immunity and a favoring of type 2 (humoral) immunity along with a highly regulated inflammatory state, particularly activated during the first and third trimester[3]. Many of the immune changes of pregnancy mimic the immune response to stress[4]. Stress increases glucocorticoid and catecholamine production, suppresses neutrophil and Natural Killer (NK) cell activity, activates release of inflammatory cytokines through the transcription factor nuclear factor kappa B (NF- κ B), and shifts immunity to a type-2 cytokine profile.[5] Many of these processes are similarly affected by pregnancy[4]. These immune responses evoked by both pregnancy and stress increase vulnerability to herpesviral reactivation [6–15].

Depressed mood may occur as an isolated transient experience or may predict the development of clinical depression. Depression is one of the most common complications in pregnancy, experienced by as many as 20 percent of pregnant women. Stress, hormonal, social, and genetic factors are involved [16–18]. Unrecognized or untreated prenatal depression contributes to suicide, which is one of the leading causes of death across the perinatal period [19, 20]. Depression is also associated with preterm labor, low birth weight, and behavioral abnormalities in the offspring [21–24].

Infections due to influenza virus, human immunodeficiency virus (HIV) and *Toxoplasma gondii* are associated with depressed mood and/or depression during pregnancy[17, 25, 26]. Additionally, in pregnant African American women, stress and depression were associated with EBV reactivation [21, 27]. These data provide evidence of a link between maternal stress, depression, and viral reactivation; however, further studies are needed to evaluate the bio behavioral pathways. Herpes simplex virus type-2 (HSV-2) IgG levels were found to be associated with depression in a large non-pregnant population(OR 2.1, 95% CI 1.5 to 2.9) [28]. Many studies on distressful psychosocial states and HSV reactivation in humans have been conducted, including studies of both oral and genital herpes, but none have included pregnant women. Most individuals infected with HSV infections are asymptomatic during viral latency in the sensory neuronal cells in which the virus resides. Latent or clinically silent periods can last for years or a lifetime. Latently infected cells may be stimulated during physiological or psychological stress or in states of immune deficiency, to increase viral transcription, resulting in the production of infectious virions which lead to either asymptomatic viral shedding or disease recurrence[29]. HSV-1 has been typically associated with oral lesions, while HSV-2 is the major cause of genital lesions. Recently more cases of HSV-1 genital herpes have been reported [30, 31]. Genital herpes is of concern during pregnancy because of the risk of transmission to the infant [31].

Based on evidence of these psychoneuroimmunological relationships during pregnancy, we proposed to test following hypothesis: Depressed mood will be positively associated with plasma levels of herpes viral immunoglobulins among pregnant women.

METHODS

Procedures

The study was a sub-study of a parent project that investigated pregnancy factors that increased risk for later postpartum thyroiditis. The pregnant women who were screened in the parent study gave informed consent and the study and sub-study were approved by the University of South Florida Institutional Review Board (IRB) prior to the collection of data. Pregnant women between 16 to 25 weeks' gestation who met inclusion criteria for the parent study were recruited from private and public obstetrical clinics in a large southern city in the U.S. from 2007 to 2011. Exclusion criteria for the parent study, determined by review of medical diagnoses listed in the medical record, included HIV or hepatitis, mental illness (clinical depression, generalized anxiety disorder, bipolar disease, or psychoses), other chronic disease, medications that affect the immune system, multiple pregnancy, use of assistive reproductive technology, and thyroid disease. While the initial goal of the parent study was to identify women at risk for thyroid disease by measuring the thyroid peroxidase antibody titer, only those women testing negative for this antibody were included in the sub-study. We had collected evidence of herpesviral IgG levels in 380 women as part of the characterization of these pregnant women's immune status. In the sub-study we subsequently had complete demographic data in 247 women to analyze in relation to herpesviral titers, PSS scores and POMS scores, which had been collected on all women in the parent study. EBV capsid antigen IgGs were available on only 199 participants.

The research data were obtained from demographic data, self-report questionnaires, and blood samples collected in clinic offices during a routine prenatal appointment.

Demographic Data

Baseline data, which were collected at the time of recruitment, included age, ethnicity, years of education, marital status, weeks of pregnancy, income, parity, the presence of any chronic or acute health problems, current medications, and body mass index (BMI).

Perceived Stress Scale (PSS)

The PSS is a 14-item instrument to evaluate cognitions and emotions related to perceived general stress that an individual felt or thought of as stressful in the week preceding the measurement. Participants completed the PSS at the time of enrollment. The PSS-14 uses a 5-point Likert-type summated rating scale response format (0 = never to 4 = very often) and has a range of 0 to 56. The PSS consistently has Cronbach's alphas between .84 and .86[32]. The PSS also has evidence of short-term test-retest reliability (.85) as well as construct validity.

Profile of Mood States (POMS)

Participants also completed the POMS[33] at the time of enrollment. The instrument provides a multi-dimensional assessment of mood states to describe how the participant had felt over the week prior to enrollment. The POMS is a 65-item, 5-point Likert-type scale (0 = not at all to 4 = extremely) and has a total mood disturbance score and 6 subscales: depression-dejection (15 items, score range 0–60), tension-anxiety, confusion-bewilderment, fatigue-inertia, anger-hostility, and vigor-activity.

The POMS has good internal consistency and moderate test-retest reliability[34]. POMS scores have alpha reliabilities from .87 to .92 and test-retest reliabilities ranging from .65 to .74 [35]. The POMS-Depression/dejection (POMS-D) measures depressed mood, and is not a depression scale. Nevertheless, we found that the POMS-D was highly correlated with Center for Epidemiological Studies Depression Scale ($r=.73$, $p<.001$) in a population of women veterans [36]. The POMS-D score was also reported to be highly correlated with the Beck Depression Scale score [34].

Blood Collection and Processing

When participants between 16 to 25 weeks of pregnancy enrolled, their peripheral blood samples (15 mL) were collected by antecubital venipuncture into heparinized vacutainer tubes, kept cold, and brought to the laboratory within two hours. The blood was centrifuged at 3800 rpm for 25 minutes at 4°C. The plasma supernatants were aliquoted and stored at –80° C. Frozen aliquots were shipped overnight in dry ice to the Stanley Virology Laboratory at Johns Hopkins School of Medicine for measurement of a panel of common herpes virus IgG antibody levels. The majority of the blood samples were taken in the morning.

Herpesviral IgG Immunoassays

HSV-1, HSV-2, HHV-6, and CMV IgG serology was performed by the solid-phase enzyme immunoassay method at the Stanley Virology laboratory at Johns Hopkins University following previously described methods[37]. EBV IgG levels were measured by antibodies to Epstein-Barr viral capsid antigen (EBV VCA) with an enzyme-linked immunosorbent assay (ELISA) followed manufacturer's (ALPCO, Salem, N.H.) directions and was performed in the investigators' laboratory. The results are expressed in terms of ratios to arbitrary standards. Values greater than 1 were considered seropositive for all IgG levels except for HHV6, which was considered seropositive if greater than 6. EBV IgG was measured by optical density ratio units and calculated according to the manufacturer's directions (ALPCO). The cut-off point for EBV was 10 and intra-assay coefficients of variation were less than 10%. The herpesviral seropositivity rates in this study were: HSV-1 (57.8%), HSV-2 (22%), HHV-6 (76.2%), CMV (60.1%), and EBV (90.7%). The entire range of IgG titers of the different herpesviruses were analyzed as continuous variables when relationships between perceived stress and depressed mood were examined. This was based on the assumption that presence of antibody might signify infection at some point in the person's life, while values above the cut point might reflect reactivation or new viral infection.

Data Analysis Plan

Using Microsoft Excel software version 2010 and Statistical Package for Social Sciences (SPSS) computer software version 22, data cleaning and data processing were performed to detect corrupt or inaccurate data. All tests of statistical significant were two-tailed and p values less than .05 were considered significant.

Univariate data analysis in this study included descriptive statistics, means and standard deviations of all the variables. All of the data were analyzed for normality, outliers, and missing data. Common logarithm (log10) transformations were performed if needed for negative skewness and outliers were checked. Log-10 transformed POMS-D scores were used to better meet the assumption of the normality. Preliminary analyses were conducted to confirm no violation of the assumptions of multicollinearity. Demographic covariates were selected based on the epidemiological literature describing demographic influences on genital herpes infection [38]. In addition, BMI was used as a covariate due to its potential relationship with maternal immunity. Bivariate data analysis included Chi-square tests, independent sample t-tests, and Pearson's product moment correlations. Multivariate data analysis included multiple regression analysis to explore the relationship between each continuous dependent variable (e.g. herpesviral IgG levels) and POMS-D score, while adjusting for demographic covariates. Independent variables were examined for collinearity and were found to be acceptable. Logistic regression was performed to determine if POMS-D was associated with seropositivity compared to seronegativity (regardless of level).

RESULTS

Description of the Sample

The participants ($N=247$) were all thyroid peroxidase antibody negative, averaging 19.8 ± 2.8 weeks of pregnancy. Even though a previous medical diagnosis of depression was used as an exclusion criteria, 10 participants (4%) had POMS-D scores over 20 at the prenatal visit at which they were enrolled suggesting possible clinical depression [34] and they were referred to their healthcare provider for further depression evaluation and treatment. Table S1 (Supplemental Digital Content 1) shows correlations of each of the herpesviral titers with selected demographics and mood and stress scores. The only herpesvirus IgG titer that was significantly correlated with POMS-D was HSV-2 ($r=.19$, $p=.003$). While several titers were highly correlated with each other, signifying co-infection, other herpesvirus titers did not have relationships with POMS or perceived stress scores, except for one relationship of CMV IgG titers and fatigue. The POMS-anger scale was also correlated with HSV-2 level ($r=.16$, $p=.012$) as was the total Mood Disturbance score ($r=.16$, $p=.012$). The other POMS subscale scores (fatigue, tension, confusion, vigor) were not correlated with HSV-2 IgG levels. HSV-1 and HSV-2 are both known to cause genital herpes and the rates of positivity in this sample mirrors the frequency reported in pregnant women in the United States [38]. Characteristics of women who were negative for HSV-2 were compared to women with positive titers (Table 1). Seropositive women were more likely to have higher BMIs, be AA, have lower income, have less education and be single. The only moods that differed significantly between seronegatives compared to seropositives were POMS-depression

($t=2.59$ ($df=245$), $p=.01$), POMS-anger ($t=2.54$ ($df=245$), $p=.01$) and the total mood disturbance.

Regression Models

Because there were missing data on some of the demographics (marital status, income) (participants chose not to disclose), the number of participants with complete data available for the regression models was 247. The data from the group with missing data ($N=133$) were compared with the data from the participants who had complete data. There were no significant differences in race, marital status or BMI. There were significant differences in viral titers, with HSV-2 IgG titers significantly higher in the group with missing data ($t=2.5$, $p=.013$) and HHV6 titers significantly lower ($t=-2.9$, $p=.003$). The POMS-D score was higher in the group with missing data ($t=2.4$, $p=.02$) as was the POMS-A scale ($t=2.3$, $p=.02$). The reason for difference was not immediately apparent, but it may be that poorer and single women were less likely to reveal this personal information.

Income was highly associated with race, age and marital status, but was not disclosed by many participants and did not contribute additional variance to the regression model when added as an imputed variable (mean substitution). BMI was available and included as a covariate due to its potential relationship with immune function. Hierarchical multiple regression was used to assess the association between depressed mood with HSV-2 IgG levels in participants with positive levels, adjusting for self-reported demographic measures (African American (AA) race, age, BMI and marital status). Race and marital status were categorical variables, while age and BMI were continuous. AA race was dichotomized to women describing themselves as AA compared to any other race. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Covariates were chosen based on a large body of literature indicating increased risk for genital herpes in African Americans, women of younger age and those of single marital status [39]. We did not have data on number of sexual partners, which is another important risk factor. These covariates were entered at step 1, explaining 19.6 % of the variance in HSV-2 IgG levels. After entry of POMS-D scores at step 2, the total variance explained by the model as a whole was 20.4% ($F(5, 239) = 13.5$, $p<.001$). In the final model AA race ($\beta = .251$, $p < .001$), older age ($\beta = .199$, $p = .002$), single marital status ($\beta = -.304$, $p < .001$) and depressed mood ($\beta = .122$, $p = .04$) was associated with HSV-2 IgG levels (Table 2). Pregnant women with higher levels of IgG antibody to HSV-2 also had greater depressed mood, when race, age, BMI and marital status were held constant.

Logistic regression was used to assess the association of a number of factors (race, marital status, age and POMS-D score) with HSV-2 seronegative vs. seropositive status. The full model containing all variables was statistically significant, $X^2(3, N=247) = 38.8$, $p < .001$ indicating that the model distinguished between those with a positive HSV-2 levels compared to negative HSV-2 levels. The model as a whole explained between 14.5% (Cox & Snell R Square) and 23% (Nagelkerke R Square) of the variance in HSV-2 levels and correctly classified 82% of the cases. All of the independent variables made unique contributions to the model, and the strongest correlate of HSV-2 was single marital status (odds ratio 4.68) followed by POMS-D scores (odds ratio 2.92). African American race had

an odds ratio of 2.58. These results suggest that single women were more than 4 times as likely as married women to be positive for HSV-2 and those with higher depressed mood, adjusting for marital status or African American race, had nearly three times greater likelihood of HSV-2 positivity (Table 3).

DISCUSSION

We were only able to confirm our hypotheses regarding depressed mood and herpes viral titers for HSV-2. There was no evidence of any relationships of mood states or perceived stress with the other four viral titers that were measured. Since HSV-2 is the cause of genital herpes, the pregnant reproductive tract may be a factor in the results. Viral IgG levels may reflect greater viral shedding from genital tissues. The titer indicates that the immune system is responding to viral components by releasing specific immunoglobulins. The reproductive tract during pregnancy may be especially sensitive to viral shedding in infected mothers. There are changes in the cervix and genital tract mucosal immunity during pregnancy that may make HSV-2 reactivation more likely [40, 41]. Women are more at risk for infections such as bacterial vaginosis which changes the microbiota of the genital tract and increases risk for viral shedding and survival [42]. In the study reported here we found an association of depressed mood and both HSV-2 seropositivity, indicating that the women were likely infected at some point in their life with the virus, and levels of HSV-2 IgG, suggesting reactivation or even primary infection. The other herpesviruses measured infect non-reproductive sites and thus may be more sequestered. The frequency of genital herpes varies greatly by race and ethnicity in pregnant women but most infected women are asymptomatic [38, 42]. The greatest risk during pregnancy of HSV-2 infection is neonatal infection acquired during birth when there is contact with viruses shed from the cells lining the birth canal [43]. Nearly 85 % of HSV-2 transmission from mother to fetus occurs during delivery, while 5 % is caused by intrauterine infection. HSV-2 infection can cause miscarriage, stillbirth, congenital herpes and neonatal herpes infections in pregnant women with primary or recurrent HSV-2 infection [44–47].

This study found that African American women had higher HSV-2 seropositive rates and greater depressed mood than non-African American women. This result was similar to Gottlieb and colleagues [48], who reported that African American women had the highest overall HSV-2 seroprevalence in a study of five sexually transmitted-disease clinics. Also, this finding was similar to Borders and colleagues [49] and Christian and colleagues [21] who reported that African American women had higher perceived stress levels and EBV levels in their studies.

Single women were significantly more likely to be infected in our study as has been shown in other epidemiological studies [50]. Age was entered as a covariate due to studies indicating that younger age at first intercourse was a risk for contracting genital herpes [39]. We did not have this information and our youngest eligible age was 18 years old. Age, however, contributed to the model in a positive direction. Age and single status may be related to the number of sexual partners, which is an important risk factor for genital herpes infection [39]. It has also been shown that HSV IgG levels become constant as women get older [50].

The underlying mechanism for these relationships cannot be determined from the current study. It is possible that women who were seropositive had experienced episodes of painful lesions and knew they were at risk for certain complications of pregnancy as well as at risk for transmitting the virus to their infants. This could be stressful and lead to depressed and angry mood. Sexually transmitted infections, including genital herpes, often lead to psychological and psychosexual morbidity [51]. This could be a possible explanation of the correlation of HSV-2 with the POMS-anger scale as well. Another possibility is that having multiple sex partners, a well-known risk factor for genital herpes, could lead to, or be a consequence of, depressed mood, so this may be a pathway rather than through immune mechanisms [28]. Thus, psychological distress can be both a cause and a consequence of HSV-2 reactivation [52].

The possibility of cellular immune suppression associated with distressful psychosocial states and situations, along with diminished cellular immune function during pregnancy itself, could also be causative and needs further exploration. Stress has been associated with diminished T-cell responses, such as reduction in cytokine production, and decreased memory T-cells and cytotoxic T-cells, which mediate killing herpes virus infected cells [53]. Elevated herpes viral IgG levels may reflect ineffective cellular immunity control over herpes viral reactivation [54]. The effect of depressed mood and HSV-2 positivity and titer was small. Clinical depression rather than mood is likely to be more a significant influence on immunological processes.

Limitations

This study was conceptualized after data had been collected in the parent study. There was missing demographic data and there were some differences between the women with missing data and those with complete data who were analyzed in the regressions. This is a limitation in that the associations found are restricted to a group that may have been different demographically. It is possible that the women with missing data did not report income and marital status because they were reluctant to disclose a socioeconomically disadvantaged state.

The choice of instruments and other measures was restricted to those used in the parent study. A major limitation is that the POMS instrument measures only mood states over the past week and not depression. Therefore the findings may represent transitory changes in mood states since we excluded women with previous history of clinical depression. Another limitation is that the study was cross-sectional with only a single blood sample and without additional immune characterizations.

Longitudinal studies are needed to link herpes viral reactivation and prenatal depression and thus better estimate the direction of causality. Measuring immune markers longitudinally might also improve our mechanistic inferences and identify more precise treatment targets for perinatal depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Glossary

PSS	Perceived Stress Scale
POMS-D	Profile of Mood States-depression
HSV-2	herpes simplex virus type-2
HSV-1	herpes simplex virus type-1
HHV-6	human herpes virus-6
CMV	cytomegalovirus
EBV	Epstein-Barr virus
EBV VCA	Epstein-Barr viral capsid antigen
ELISA	enzyme-linked immunosorbent assay
BMI	body mass index
AA	African American

References

1. Chen SJ, Liu YL, Sytwu HK. Immunologic regulation in pregnancy: From mechanism to therapeutic strategy for immunomodulation. *Clin Dev Immunol*. 2012; 2012:258391. [PubMed: 22110530]
2. Rusterholz C, Hahn S, Holzgreve W. Role of placentally produced inflammatory and regulatory cytokines in pregnancy and the etiology of preeclampsia. *Seminars in immunopathology*. 2007; 29:151–162. [PubMed: 17621700]
3. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. *N Engl J Med*. 2014; 370:2211–2218. [PubMed: 24897084]
4. Schminkey DL, Groer M. Imitating a stress response: A new hypothesis about the innate immune system's role in pregnancy. *Med Hypotheses*. 2014; 82:721–729. [PubMed: 24698849]
5. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: Implications for health. *Nat Rev Immunol*. 2005; 5:243–251. [PubMed: 15738954]
6. Bao AM, Meynen G, Swaab DF. The stress system in depression and neurodegeneration: Focus on the human hypothalamus. *Brain Res Rev*. 2008; 57:531–553. [PubMed: 17524488]
7. Black PH. Immune system-central nervous system interactions: Effect and immunomodulatory consequences of immune system mediators on the brain. *Antimicrob Agents Chemother*. 1994; 38:7–12. [PubMed: 8141583]
8. Godbout JP, Glaser R. Stress-induced immune dysregulation: Implications for wound healing, infectious disease and cancer. *J Neuroimmune Pharmacol*. 2006; 1:421–427. [PubMed: 18040814]
9. Hansel A, Hong S, Camara RJ, von Kanel R. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. *Neurosci Biobehav Rev*. 2010; 35:115–121. [PubMed: 20026349]
10. Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: Translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology*. 2012; 37:137–162. [PubMed: 21918508]

11. Maes M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011; 35:664–675. [PubMed: 20599581]
12. Messay B, Lim A, Marsland AL. Current understanding of the bi-directional relationship of major depression with inflammation. *Biol Mood Anxiety Disord*. 2012; 2:4. [PubMed: 22738397]
13. Padgett DA, Glaser R. How stress influences the immune response. *Trends Immunol*. 2003; 24:444–448. [PubMed: 12909458]
14. Segerstrom SC, Miller GE. Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychol Bull*. 2004; 130:601–630. [PubMed: 15250815]
15. Sperner-Unterwieser B, Kohl C, Fuchs D. Immune changes and neurotransmitters: Possible interactions in depression? *Prog Neuropsychopharmacol Biol Psychiatry*. 2014; 48:268–276. [PubMed: 23085509]
16. Bonari L, Pinto N, Ahn E, Einarson A, Steiner M, Koren G. Perinatal risks of untreated depression during pregnancy. *Can J Psychiatry*. 2004; 49:726–735. [PubMed: 15633850]
17. Groer MW, Yolken RH, Xiao JC, Beckstead JW, Fuchs D, Mohapatra SS, Seyfang A, Postolache TT. Prenatal depression and anxiety in toxoplasma gondii-positive women. *Am J Obstet Gynecol*. 2011; 204:433, e431–437. [PubMed: 21345406]
18. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*. 2009; 65:732–741. [PubMed: 19150053]
19. Lindahl V, Pearson JL, Colpe L. Prevalence of suicidality during pregnancy and the postpartum. *Arch Womens Ment Health*. 2005; 8:77–87. [PubMed: 15883651]
20. Oates M. Suicide: The leading cause of maternal death. *Br J Psychiatry*. 2003; 183:279–281. [PubMed: 14519602]
21. Christian LM. Psychoneuroimmunology in pregnancy: Immune pathways linking stress with maternal health, adverse birth outcomes, and fetal development. *Neurosci Biobehav Rev*. 2012; 36:350–361. [PubMed: 21787802]
22. Field T, Diego M, Hernandez-Reif M. Prenatal depression effects and interventions: A review. *Infant Behav Dev*. 2010; 33:409–418. [PubMed: 20471091]
23. Gennaro S, Hennessy MD. Psychological and physiological stress: Impact on preterm birth. *J Obstet Gynecol Neonatal Nurs*. 2003; 32:668–675.
24. Markham JA, Koenig JI. Prenatal stress: Role in psychotic and depressive diseases. *Psychopharmacology (Berl)*. 2011; 214:89–106. [PubMed: 20949351]
25. Hsu PC, Groer M, Beckie T. New findings: Depression, suicide, and toxoplasma gondii infection. *J Am Assoc Nurse Pract*. 2014; 26:629–637. [PubMed: 24715687]
26. Ross R, Sawatphanit W, Zeller R. Depressive symptoms among hiv-positive pregnant women in thailand. *J Nurs Scholarsh*. 2009; 41:344–350. [PubMed: 19941579]
27. Haeri S, Johnson N, Baker AM, Stuebe AM, Raines C, Barrow DA, Boggess KA. Maternal depression and epstein-barr virus reactivation in early pregnancy. *Obstet Gynecol*. 2011; 117:862–866. [PubMed: 21422857]
28. Pratt LA, Xu F, McQuillan GM, Robitz R. The association of depression, risky sexual behaviours and herpes simplex virus type 2 in adults in nhanes, 2005–2008. *Sex Transm Infect*. 2012; 88:40–44. [PubMed: 22057015]
29. Aranda AM, Epstein AL. herpes simplex virus type 1 latency and reactivation: An update. *Medecine sciences : M/S*. 2015; 31:506–514. [PubMed: 26059301]
30. Glinsek Biskup U, Ursic T, Petrovec M. Laboratory diagnosis and epidemiology of herpes simplex 1 and 2 genital infections. *Acta Dermatovenerol Alp Pannonica Adriat*. 2015; 24:31–35. [PubMed: 26086165]
31. Stephenson-Famy A, Gardella C. Herpes simplex virus infection during pregnancy. *Obstet Gynecol Clin North Am*. 2014; 41:601–614. [PubMed: 25454993]
32. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983; 24:385–396. [PubMed: 6668417]
33. McNair, D.; Droppleman, L. Profile of mood states manual. North Tonawanda, NY: Multi-Health systems; 1992.

34. Griffith NM, Szaflarski JP, Szaflarski M, Kent GP, Schefft BK, Howe SR, Privitera MD. Measuring depressive symptoms among treatment-resistant seizure disorder patients: Poms depression scale as an alternative to the bdi-ii. *Epilepsy Behav.* 2005; 7:266–272. [PubMed: 16005686]
35. Cruess S, Antoni M, Cruess D, Fletcher MA, Ironson G, Kumar M, Lutgendorf S, Hayes A, Klimas N, Schneiderman N. Reductions in herpes simplex virus type 2 antibody titers after cognitive behavioral stress management and relationships with neuroendocrine function, relaxation skills, and social support in hiv-positive men. *Psychosom Med.* 2000; 62:828–837. [PubMed: 11139003]
36. Duffy AR, Beckie TM, Brenner LA, Beckstead JW, Seyfang A, Postolache TT, Groer MW. Relationship between toxoplasma gondii and mood disturbance in women veterans. *Military medicine.* 2015; 180:621–625. [PubMed: 26032378]
37. Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Ruslanova I, Yolken RH. Association of serum antibodies to herpes simplex virus 1 with cognitive deficits in individuals with schizophrenia. *Arch Gen Psychiatry.* 2003; 60:466–472. [PubMed: 12742867]
38. Xu F, Markowitz LE, Gottlieb SL, Berman SM. Seroprevalence of herpes simplex virus types 1 and 2 in pregnant women in the united states. *American journal of obstetrics and gynecology.* 2007; 196:43, e41–46. [PubMed: 17240228]
39. Halioua B, Malkin JE. Epidemiology of genital herpes - recent advances. *Eur J Dermatol.* 1999; 9:177–184. [PubMed: 10210781]
40. Anderson BL, Mendez-Figueroa H, Dahlke JD, Raker C, Hillier SL, Cu-Uvin S. Pregnancy-induced changes in immune protection of the genital tract: Defining normal. *Am J Obstet Gynecol.* 2013; 208:321, e321–329. [PubMed: 23313311]
41. Kalinka J, Krajewski P, Sobala W, Wasiela M, Brzezinska-Blaszczek E. The association between maternal cervicovaginal proinflammatory cytokines concentrations during pregnancy and subsequent early-onset neonatal infection. *J Perinat Med.* 2006; 34:371–377. [PubMed: 16965223]
42. Jayaram A, Orfanelli T, Doulaveris G, Linhares IM, Ledger WJ, Witkin SS. Autophagy and female genital tract infections: New insights and research directions. *BJOG : an international journal of obstetrics and gynaecology.* 2014; 121:801–808. [PubMed: 24506514]
43. Gardella C, Brown Z. Prevention of neonatal herpes. *BJOG : an international journal of obstetrics and gynaecology.* 2011; 118:187–192. [PubMed: 21159118]
44. Avgil M, Ornoy A. Herpes simplex virus and epstein-barr virus infections in pregnancy: Consequences of neonatal or intrauterine infection. *Reproductive toxicology (Elmsford, NY).* 2006; 21:436–445.
45. Pereira DB, Antoni MH, Danielson A, Simon T, Efantis-Potter J, Carver CS, Duran RE, Ironson G, Klimas N, Fletcher MA, O'Sullivan MJ. Stress as a predictor of symptomatic genital herpes virus recurrence in women with human immunodeficiency virus. *J Psychosom Res.* 2003; 54:237–244. [PubMed: 12614833]
46. Perozzi KJ, Zalace KK, Howard V, Skariot L. Hsv: What you need to know to care for your pregnant patient. *MCN Am J Matern Child Nurs.* 2007; 32:345–350. quiz 351–342. [PubMed: 17968215]
47. Straface G, Selmin A, Zanardo V, De Santis M, Ercoli A, Scambia G. Herpes simplex virus infection in pregnancy. *Infect Dis Obstet Gynecol.* 2012; 2012:385697. [PubMed: 22566740]
48. Gottlieb SL, Douglas JM Jr, Schmid DS, Bolan G, Iatesta M, Malotte CK, Zenilman J, Foster M, Baron AE, Steiner JF, Peterman TA, Kamb ML. Seroprevalence and correlates of herpes simplex virus type 2 infection in five sexually transmitted-disease clinics. *J Infect Dis.* 2002; 186:1381–1389. [PubMed: 12404152]
49. Borders AE, Grobman WA, Amsden LB, McDade TW, Sharp LK, Holl JL. The relationship between self-report and biomarkers of stress in low-income reproductive-age women. *Am J Obstet Gynecol.* 2010; 203:577, e571–578. [PubMed: 20870203]
50. Malkin JE, Morand P, Malvy D, Ly TD, Chanzy B, de Labareyre C, El Hasnaoui A, Hercberg S. Seroprevalence of hsv-1 and hsv-2 infection in the general french population. *Sex Transm Infect.* 2002; 78:201–203. [PubMed: 12238654]

51. Mindel A, Marks C. Psychological symptoms associated with genital herpes virus infections: Epidemiology and approaches to management. *CNS drugs*. 2005; 19:303–312. [PubMed: 15813644]
52. Strachan E, Saracino M, Selke S, Magaret A, Buchwald D, Wald A. The effects of daily distress and personality on genital hsv shedding and lesions in a randomized, double-blind, placebo-controlled, crossover trial of acyclovir in hsv-2 seropositive women. *Brain, behavior, and immunity*. 2011; 25:1475–1481.
53. Khanna KM, Lepisto AJ, Decman V, Hendricks RL. Immune control of herpes simplex virus during latency. *Curr Opin Immunol*. 2004; 16:463–469. [PubMed: 15245740]
54. Fagundes CP, Glaser R, Alfano CM, Bennett JM, Povoski SP, Lipari AM, Agnese DM, Yee LD, Carson WE 3rd, Farrar WB, Malarkey WB, Kiecolt-Glaser JK. Fatigue and herpesvirus latency in women newly diagnosed with breast cancer. *Brain Behav Immun*. 2012; 26:394–400. [PubMed: 21988771]

TABLE 1

Comparison of the HSV-2 Seropositive and Negative Groups on Demographic Characteristics and Psychosocial Measures

Variable	HSV-2(-) <i>N</i> =198	HSV-2(+) <i>N</i> =49
Age (years)	27.68 (5.28)	28.37 (4.75)
African American	34 (17)	22 (44)
Income \$25,000 *	48 (24)	18 (37)
Education High School **	87 (44)	29 (60)
Marital Status		
Single	53 (27)	30 (63)
Married	145 (73)	18 (37)
BMI (kg/ m ²)	26.39 (6.97)	32.61 (29.19)
POMS-Anxiety	7.79 (4.63)	8.89 (5.92)
POMS-Depression	4.05 (5.66)	8.08 (10.55)
POMS-Anger	5.25 (5.62)	8.16 (7.55)
POMS-Vigor	14.15 (6.24)	13.43 (5.67)
POMS-Fatigue	7.46 (4.94)	9.31 (6.30)
POMS-Confusion	5.60 (3.80)	7.04 (4.70)
POMS-Total	15.83 (22.13)	28.05 (34.15)
PSS	21.45 (7.1)	22.75 (7.50)

Data are presented as mean (SD) or *n* (%)

Note. HSV-2(-): Herpes simplex virus type 2 seronegative, HSV-2(+): Herpes simplex virus type 2 seropositive, *M*: Mean, *SD*: Standard deviation, %: Percentage, BMI: Body mass index, POMS: Profile of Mood States, PSS: Perceived Stress Scale

*
N=199,

**
N=162

TABLE 2

Multivariate Models of Measures Associated with HSV-2 during Pregnancy

Variable	Step 1			Step 2		
	B	SE B	β	B	SE B	β
Intercept	-.051	.097		-.108	.100	
Age	.011	.003	.195	.011	.003	.199
Marital Status	-.193	.037	-.325	-.181	.038	-.304
AA	.173	.041	.255	.170	.040	.251
BMI [#]	.001	.001	.074	.002	.001	.079
POMS-D				.077	.037	.122
	$R = .454$			$R = .470$		
	Adjusted $R^2 = .196$			Adjusted $R^2 = .204$		
	$F(4, 240) = 15.56^{***}$			$F(5, 239) = 13.5^{***}$		
	F change (1, 239) = 4.39*					

Note. AA: African American, BMI: Body mass index, POMS-D: Profile of Mood States Depression

[#] Missing BMI data in 2 cases

* $p = .025$,

*** $p < .001$

TABLE 3

Logistic Regression of HSV-2 Seropositives and Seronegatives (N=245)

Variable	B	S.E.	Wald	df	p	O.R	95% C.I.	
							Lower	Upper
Age	.110	.039	7.97	1	.005	1.12	1.03	1.21
BMI [#]	.026	.026	.98	1	.322	1.03	.96	1.08
Black	.949	.429	4.90	1	.027	2.58	1.11	5.98
Single	1.540	.416	13.75	1	.000	4.68	.09	.48
POMS-D	1.070	.411	6.80	1	.009	2.92	1.31	6.54
Constant	-6.890	1.410	24.02	1	.001			

Note. BMI: Body mass index, Single: Marital Status, POMS-D: Profile of Mood States- Depression

[#]Missing BMI data in 2 cases