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POSTTRAUMATIC STRESS DISORDER, SMOKING, AND CORTISOL IN A COMMUNITY SAMPLE OF PREGNANT WOMEN

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Abstract

The prevalence of posttraumatic stress disorder (PTSD) in the United States is higher among pregnant women than women generally. PTSD is related to adverse birth outcomes via physiological and behavioral alterations, such as smoking. We utilize salivary cortisol measures to examine how traumatic stress, smoking and the hypothalamic-pituitary-adrenal axis interact. Pregnant women (n=395) gave cortisol specimens as part of a cohort study of PTSD and pregnancy at three health systems in the Midwestern United States. Women were divided into three groups: nonsmokers, quitters (who stopped smoking during pregnancy), and pregnancy smokers. Mean cortisol values at three points, sociodemographics, trauma history, and PTSD were compared across groups. We assessed the association of smoking group and PTSD with late afternoon cortisol levels. Smokers, quitters, and nonsmokers differed on demographic risk factors and PTSD symptom load. Late afternoon and bedtime cortisol measures were significantly positively correlated with smoking in pregnancy, with smokers with PTSD presenting the highest cortisol levels. Regression analysis showed that smoking in pregnancy was associated with higher late afternoon cortisol in an additive manner with PTSD symptoms. Smoking appears to have a different relationship with cortisol level for those with and without PTSD. This is the first study to show additive effects of smoking and PTSD on cortisol levels in pregnant women. Since high cortisol, smoking, and PTSD have been shown to adversely affect perinatal outcomes, and since

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those continuing to smoke in pregnancy had the highest PTSD symptom load, PTSD-specific smoking cessation programs in maternity settings are warranted.

Keywords

Tobacco use; pregnancy; PTSD; cortisol; trauma

1. Introduction

1.1. Posttraumatic Stress Disorder, Smoking, and Pregnancy Complications

The prevalence of posttraumatic stress disorder (PTSD) in the United States is twice as high among pregnant women than women generally (Seng, Low, Sperlich, Ronis, & Liberzon, 2009). PTSD is related to pregnancy complications, including ectopic pregnancy and spontaneous abortion (Seng et al., 2001), and in a recent prospective study, predicted shorter gestation and lower birth weight (Seng, Kane Low, Sperlich, Ronis, & Liberzon, 2011). These adverse outcomes may result via physiological or behavioral alterations stemming from the traumatic experience or from PTSD (Seng et al., 2001). PTSD is also associated with cigarette smoking while pregnant (Lopez, Konrath, & Seng, 2011), a behavioral alteration with adverse perinatal outcomes (Cnattingius, 2004). Given that PTSD has only recently been determined to be a risk factor for adverse perinatal outcomes, studies of potential physiological and behavioral pathways are needed. The purpose of this study is to augment previous findings that (1) PTSD is associated with elevated cortisol across the day in pregnant women (Seng et al., under review) and (2) women with PTSD are more likely to continue smoking during pregnancy (Lopez et al., 2011).

1.2. Pregnancy, Smoking, and PTSD

Smoking is well known to affect the HPA axis, with smoking associated with acute increases in cortisol (Kirschbaum, Scherer, & Strasburger, 1994; Kirschbaum, Wust, & Strasburger, 1992) and smokers presenting higher basal cortisol concentrations across the day (Badrick, Kirschbaum, & Kumari, 2007; Direk, Newson, Hofman, Kirschbaum, & Tiemeier, 2011; Field, Colditz, Willett, Longcope, & McKinlay, 1994; Steptoe & Ussher, 2006). Though approximately 16% of pregnant women in the United States smoke (Substance Abuse and Mental Health Services Administration, 2013), few studies have considered cortisol concentrations among pregnant smokers, with some studies excluding smokers from sampling or analysis (e.g., Kaasen et al., 2012; La Marca-Ghaemmaghami et al., 2013; Voegtline et al., 2013), not mentioning cigarette use (e.g., Valladares, Peña, Ellsberg, Persson, & Högberg, 2009), or controlling for smoking without further investigation (e.g., Bolten et al., 2011). Smoking prior to pregnancy increases the odds of infertility, and smoking while pregnant is associated with negative perinatal health outcomes (see Cnattingius, 2004 for a review on smoking and pregnancy), including low birth weight (Brooke, Anderson, Bland, Peacock, & Stewart, 1989), a major determinant of neonatal health (McCormick et al., 1990).

Causes for maternal smoking are difficult to establish. Smoking in general occurs at higher rates in low-income populations (Dube et al., 2010), and addiction-related factors, such as

the number of cigarettes smoked prior to pregnancy, (Olsen, 1993; Severson, Andrews, Lichtenstein, Wall, & Zoref, 1995), a history of heavy smoking, and an earlier age at first use (Cnattingius, 2004) also appear to influence continued smoking during pregnancy. Perceptions of more life stress, stressful life events during pregnancy, perceived lack of control over life, and having an unemployed partner are also related to smoking while pregnant (Bullock, Mears, Woodcock, & Record, 2001; Dejin-Karlsson et al., 1996).

Studies with pregnant survivors of sexual abuse trauma (Grimstad & Backe, 1998) and with pregnant women with PTSD (Morland et al., 2007; Smith, Poschman, Cavaleri, Howell, & Yonkers, 2006) find associations of abuse history and PTSD with smoking during pregnancy. In comparisons of women who continue to smoke during pregnancy with those who quit, Lopez, Konrath, and Seng (2011) find that pregnant smokers are more likely to have current and lifetime PTSD diagnoses, have more instances of previous abuse trauma, and, are more likely to endorse having used tobacco to “cope with emotions or problems.”

1.3. Cortisol Alterations: PTSD and Pregnancy

Individuals with PTSD experience alterations to stress regulation systems, including the hypothalamic-pituitary-adrenal (HPA) axis (Selye, 1956). Attempts to understand alterations to the HPA axis when stress disorders are of interest utilize cortisol as a measure of HPA axis functioning (Marin, Martin, Blackwell, Stetler, & Miller, 2007). These have yielded mixed results, with some studies finding no difference in basal cortisol levels of those with and without PTSD (Altemus & Cloitre, 2003; Halbreich et al., 1989; Tucker et al., 2004), while others found lower (Yehuda, 2001) or higher levels (Lindauer, Olff, van Meijel, Carlier, & Gersons, 2006).

Among pregnant women, research on the relationships between stress and cortisol has similarly yielded mixed results. Obel et. al. (2005) find higher evening levels of salivary cortisol in late pregnancy among women who experienced stressful life events. Valladares, Peña, Ellsberg, Persson, and Högberg (2009) find higher levels of salivary cortisol associated with partner violence during pregnancy and maternal stress. On the other hand, Bolten et. al. (2011) find no differences in salivary cortisol concentrations based on pregnancy or non-pregnancy related distress, and Voegtline et al. (2013) find that self-report of mental distress is not associated with significant variation in salivary cortisol among pregnant women. Data from our studies of pregnant women, including findings from this data set published elsewhere (Seng et al., under review) and previous preliminary work (Seng, Low, Ben-Ami, & Liberzon, 2005), have found flatter diurnal curves among women with PTSD (i.e., lower morning peak and higher late afternoon and bedtime levels). Obel et. al. (2005), find the highest evening cortisol levels among stressed women who also smoked. Unclear patterns may be due to factors co-occurring with PTSD that may influence cortisol concentrations, such as smoking (Olff et al., 2006).

Pregnancy itself alters HPA axis functioning, with the placenta and fetus contributing to maternal circulating cortisol, especially in late gestation (Challis & Patrick, 1983; Challis, Sprague, & Patrick, 1983). For this reason, pregnancy-specific studies of the effects of PTSD and smoking on cortisol levels are needed. Methods that consider altered protein binding (Vining, McGinley, Maksvytis, & Ho, 1983) by using salivary cortisol and that

consider the gestational increase by collecting specimens prior to the rise will have the greatest likelihood of providing results comparable to studies with non-pregnant women.

1.4. The current study

Trauma-informed smoking cessation programs seem strongly warranted, especially in the context of maternity care, where the adverse outcomes of smoking are so personally and economically costly to mothers and children. A better understanding of the physiological relationships among smoking, PTSD, and the HPA axis could provide information to bolster such efforts.

A first step toward addressing these relationships can be accomplished with a secondary analysis of data from the STACY Project (NIH R01 NR008767, PI: Seng), a psychobiological study of the effects of PTSD on pregnancy outcomes. These data include diurnal salivary cortisol levels collected prior to 25 weeks gestation from a demographically diverse community sample of women in prenatal care who were well-characterized in terms of trauma history and PTSD diagnosis.

We proceed with two research questions: 1) Is smoking status associated with increased salivary cortisol concentrations among pregnant women? 2) Is this relationship affected by PTSD, and if so, how? We take into account three distinct smoking groups: nonsmokers, quitters, and pregnancy smokers.

2. Data and Methods

2.1 Description of the Parent Study

This study is a secondary analysis of a sub-sample of data from a prospective, three-cohort study of the effects of PTSD on pregnancy outcomes (NIH NR008767, PI: Seng).

Questionnaire data for this analysis are from the initial survey conducted prior to 28 weeks gestation. Procedures for the parent study (Seng et al., 2009) and for cortisol collection (Seng et al., 2008) are described briefly below.

2.2. Recruitment and Interview

Obstetric clinic nurses in eight maternity clinics at three health systems in the Midwestern United States determined eligibility (age 18 or older, expecting a first infant, able to speak English without an interpreter, and gestational age fewer than 28 weeks) from new patient history and invited women to take part in a telephone survey about “stressful things that happen to women, emotions, and pregnancy.” An organization specializing in survey research (DataStat, Ann Arbor, Michigan) conducted the interviews from August 2005 through October 2007. Interviewers verified eligibility and continued with a verbal informed consent process before explaining the Certificate of Confidentiality. All involved health systems granted Institutional Review Board approval. Interviewers conducted by phone a standardized psychiatric diagnostic interview that lasted about 33 minutes a piece. Participants were paid \$20 via check. Researchers used a computerized algorithm to assess PTSD diagnostic criteria using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV; American Psychiatric Association, 1994). Women who fit one of

three cohorts were enrolled for follow-up: PTSD-diagnosed (lifetime, $n = 319$), trauma-exposed patients without PTSD diagnosis ($n = 380$), and non-exposed controls ($n = 350$).

2.3 Questionnaire Instruments

Trauma history was assessed using a modified version of the Life Stressor Checklist (Cusack, Falsetti, & de Arellano, 2002; Wolfe & Kimerling, 1997). Lifetime and current (past month) PTSD symptoms and diagnoses were obtained using the National Women's Study PTSD module (Resnick, Kilpatrick, & Dansky, 1993). This telephone interview was used in the largest epidemiological study of PTSD in women, and has high sensitivity (0.99) and specificity (0.79) to PTSD compared to the Structured Clinical Interview for DSM-IV (Kilpatrick et al., 1994). Demographic and smoking data were gathered using the Centers for Disease Control and Prevention (CDC) Prenatal Risk Assessment and Monitoring System (PRAMS) survey (Beck et al., 2002). Living in a high crime area was coded as above or below the average U.S. crime rate based on statistics from the Federal Bureau of Investigation Uniform Crime Report in 2000 and the woman's zip code (simplymaps.com, retrieved May 20, 2009). A sociodemographic risk index was calculated using the sum of low income, high school education or less, African American race, being pregnant as a teen, and living in a zip code with a higher than average crime rate, resulting in a score ranging from 0 to 5.

2.4 Cortisol Specimens

When a survey respondent was enrolled for follow-up, she was invited to participate in the saliva specimen procedure and provided with additional informed consent and verbal instructions by the interviewer. The specimen collection kit included Salivette tubes (Sarstedt, Newton, North Carolina), an instruction sheet at seventh grade reading level, a toll-free contact number, a checklist to inquire about eating, smoking, and timing of specimen collection, and a health checklist to inquire about conditions and medications. Participants deposited saliva specimens into Salivette tubes at three time points: upon awaking, late afternoon, and at bedtime. They sealed these tubes in an envelope addressed to the lab and were paid \$20. Of the 1,049 women enrolled for follow-up, 43% returned kits ($n = 449$) (Seng et al., under review).

2.5. Data Cleaning

We began with 449 participants. First, we deleted two participants with endocrine disorders (i.e., diabetes) and nine who used medications that could be threats to internal validity (e.g., corticosteroid asthma inhalers, selective serotonin reuptake inhibitors). Next, because cortisol rises in the latter parts of pregnancy (Challis & Patrick, 1983; Challis et al., 1983), and based on a receiver operator characteristic analysis, we deleted 54 women who returned kits at greater than 25 weeks gestational age or if gestational age was unknown. We substituted the detectable limit of 0.003 $\mu\text{g/dL}$ of cortisol (morning $n = 0$ substitutions; late afternoon $n = 41$ substitutions; bedtime $n = 42$ substitutions) for cortisol specimens below the detectable limit. This resulted in 395 participants who returned at least one tube, or 392 morning, 387 late afternoon, and 394 bedtime specimens. This is $\leq 2\%$ missing data at each time point, so we did not impute cortisol values.

2.6. Smoking Classification

We divided women into one of three mutually exclusive groups based on previous and current smoking behaviors: nonsmokers, or participants who reported no cigarette use before or during pregnancy ($n = 321$); quitters, or participants who reported cigarette use prior to, but not during, pregnancy ($n = 45$); and pregnancy smokers, or participants who reported any cigarette use during pregnancy ($n = 29$).

2.7 Analysis Plan

Throughout this paper we present descriptive data in natural units ($\mu\text{g/dL}$) but report hypothesis tests using log-transformed data. We began by comparing smoking groups' profiles on demographics, trauma exposures, PTSD symptoms and diagnosis, and cortisol measures using one-way analyses of variance (ANOVA) for interval-level variables and chi-square tests for nominal variables. We focused our analyses on late afternoon cortisol levels because they were most strongly associated with PTSD in our preliminary work (King, Leichtman, Abelson, Liberzon, & Seng, 2008). We assessed correlations of smoking categories with cortisol using ρ since we judged the nonsmoker, quitter, and pregnancy smoker categories to have an ordinal or rank relationship. We used ANOVA to compare late afternoon cortisol by smoking group at each time point. Our multivariate analysis included a regression model to consider the relative effects of sociodemographic risk, smoking group, and PTSD on cortisol and assess if PTSD mediates the effect of smoking on cortisol levels. Finally, we stratified by PTSD diagnosis and re-evaluated the association of smoking with cortisol via ANOVA to determine if the pattern differs for PTSD-diagnosed women.

3. Results

3.1. Sample Description

The sample consisted of 395 participants, including 321 participants who never smoked, 45 women who smoked prior to but not during pregnancy, and 29 women who smoked in pregnancy. Table 1 compares these groups. Results for pregnancy smokers and quitters were generally similar, with the exception of current PTSD diagnosis, in which quitters were more similar to nonsmokers. The correlation of smoking category with late afternoon cortisol was weak but statistically significant ($\rho(385) = .123, p = .016$).

3.1.1. Cortisol concentrations—ANOVA tests showed significant differences in late afternoon ($F(2, 384) = 4.13, p = .017$) and bedtime cortisol measures ($F(2, 391) = 5.11, p = .006$), with women who smoked during pregnancy showing higher cortisol concentrations at both times than nonsmokers and quitters (per post hoc Scheffe test, $p < .05$). Smokers had higher and flatter cortisol curves across the day, amounting to greater overall cortisol exposure.

3.2. Multivariate Analyses

We used linear regression to assess the relationships between late afternoon cortisol level and SES risk index, dummy coded status as a pregnancy smoker or quitter (with non-smokers as reference), and lifetime PTSD symptom count. Being in the smoking group ($\beta = .$

110, $p = .037$) and PTSD symptoms ($\beta = .119$, $p = .025$) significantly predicted late afternoon cortisol level ($F = 3.54$, $p = .007$, $R^2 = .036$), while SES risk index did not.

We then followed Baron & Kinney's (1986) approach to test whether PTSD would mediate the association of smoking with cortisol level. After adjusting for SES risk, smoking was associated with PTSD symptoms ($\beta = .231$, $p < .001$). PTSD symptoms were associated with cortisol level ($\beta = .144$, $p = .005$), and smoking was associated with cortisol level ($\beta = .139$, $p = .006$). This last association was only slightly attenuated when PTSD was added to the regression, decreasing the beta for smoking to .112 ($p = .032$), suggesting a small amount of shared variance in an additive relationship.

We then stratified the sample by PTSD diagnosis, comparing women without PTSD ($n=281$) and those with PTSD ($n=106$) on late afternoon cortisol levels by smoking group using ANOVA. The bar graphs (Figure 1) showed that those without PTSD have different cortisol concentration patterns than the PTSD-diagnosed group. There is no statistically significant difference across smoking groups among those who did not have PTSD ($F(2, 278) = 2.31$, $p = .102$). Among those with PTSD, pregnancy smokers (mean 0.257, SD 0.322) and quitters (mean 0.086, SD 0.076) significantly differed from each other group per post hoc Scheffe test ($F(2, 103) = 4.51$, $p = .013$). Further investigation to compare smoking groups within the PTSD-diagnosed group showed that smokers had higher overall PTSD symptom levels than quitters (7.4 versus 5.8) and higher arousal symptoms in particular (2.4 versus 1.5), although these differences were not significant.

4. Discussion

In this study, as in others, women with a history of traumatic experiences (Grimstad & Backe, 1998; Kim, Harrison, Godecker, & Muzyka, 2013; Morland et al., 2007) and more sociodemographic stressors (Bullock et al., 2001; Dejin-Karlsson et al., 1996) were more likely to smoke in pregnancy and to meet lifetime PTSD diagnostic criteria. Smoking status predicted elevated late afternoon cortisol among pregnant women, similar to findings by Obel et al. (2005). However, it is the women who are both diagnosed with PTSD *and* continue to smoke in pregnancy who have the most elevated levels of late afternoon cortisol (mean = 0.257, SD = .175), placing them more than a standard deviation above the mean of the sample as a whole (mean = 0.107, SD = 0.122).

This study highlights an area where a behavioral alteration associated with PTSD (i.e., smoking) and a physiological one (i.e., elevated cortisol) are combining within the PTSD-diagnosed group in a way that may contribute to adverse perinatal outcomes. Although more research is warranted, these findings suggest that maternity care settings should consider providing PTSD-specific smoking cessation programs to pregnant smokers who screen positive for PTSD as a means to address two inter-related risk factors in tandem.

An important research question we cannot address with secondary analysis is the phenomenological one: Why do women with PTSD continue smoking despite all the pressure to quit during pregnancy? We can advance some ideas for future study. The HPA axis functions to mobilize the body to engage in flight or fight resource utilization, with cortisol participating in a negative feedback loop to prevent further mobilization and return

to homeostasis. Perhaps it is the “feeling” of stressors being addressed (i.e., increased cortisol engaging the negative feedback loop) that pushes women with PTSD to continue smoking in pregnancy, while those without PTSD feel no comparative soothing effect (that is, no similar increase in cortisol). Some emerging research lends credence to this hypothesis. In a study of smokers with PTSD, Dedert et al. (2013) utilize ecological momentary assessment (EMA) to consider why smokers with PTSD relapse more quickly than those without and suggest that PTSD symptoms trigger craving during periods of smoking abstinence. In our analysis of smoking in the full sample from the parent study (not reduced by saliva specimen participation; Lopez, Konrath, and Seng, 2011) we find that the use of smoking “to cope with emotions or problems” more than doubles the odds of continued smoking in pregnancy. In light of the current study, perhaps further investigation is warranted to compare the subjective experience of smoking with the cortisol response. It is possible that women with lifetime PTSD who are pregnant continue to smoke because they experience the soothing effects of elevated cortisol on the stress response system that comes with continued smoking.

A better understanding of the cause-and-effect order of smoking, cortisol release, and inhibition of the stress response system, along with qualitative descriptions of women’s psychosomatic experiences of smoking, may inform PTSD-specific smoking cessation strategies. Limitations of this study can be addressed by using larger samples and longitudinal measures so that causal directions can be better understood. Adding cortisol measures to EMA studies (i.e., Beckham et al., 2005; Dedert et al., 2013) would enhance understanding of the interrelationships of symptoms, hormone levels, and behavior.

Other limitations to this study make replication a priority. This is a secondary analysis in a study in which smoking was measured with a single self-report item, albeit a standard one used by the CDC for risk behavior surveillance. The sample size was not determined to optimize comparisons among smoking groups, and thus included a relatively small number of smokers and did not permit modeling of more rare covariates that might be important, such as comorbid drug or alcohol use. Finally, pregnancy affects physiology across numerous systems that interact with the HPA axis, so the patterns and levels found in this study may not generalize to non-pregnant women or to men.

4.1 Conclusion

Smoking in pregnancy does not exist isolated from environmental factors. Recent work has underscored pregnancy as a time in which gender-based violence and posttraumatic stress can shape maternity care and pregnancy outcomes (Munro, Foster Rietz, & Seng, 2012; Seng et al., 2011; Smit, Jonhedijk, Heres, Dolman, & Honig, 2012), possibly through behavioral alterations. The current study further shows that PTSD may cause smoking to affect pregnant women differently, increasing more dramatically the cortisol levels of those with PTSD. Whenever possible, smoking cessation interventions should be trauma-informed, and PTSD-affected people may need trauma-specific programs (<http://www.samhsa.gov/ntic/>). Multidisciplinary interventions could further address the co-occurring disorders, addictions, psychosocial stressors, poverty, and domestic violence that

may make smoking cessation during pregnancy more difficult and coping behavior seem more necessary (Lundquist, Seward, Bryatt, Tonelli, & Kolodziej, 2012).

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Highlights

Among women who smoke in pregnancy, those with PTSD have the highest cortisol levels.

This study shows additive effects of smoking and PTSD on pregnancy cortisol.

Research on PTSD somatic experience, smoking, and cortisol might inform intervention.

PTSD-specific smoking cessation strategies may help more pregnant women quit smoking.

Figure 1.

ANOVA comparisons of late afternoon cortisol levels across smoking groups with the sample stratified by PTSD diagnostic status. Bar graphs depict natural units (ug/dL) while test uses log-transformed values.

Table 1

Sociodemographic risk and mental health factors by group.

	Nonsmokers (n=321)	Quitters (n=45)	Smokers (n=29)	χ^2/F
Demographics				
	% (n) or mean (SD)			
African American %(n)	28.3 (91)	55.6 (25)	55.2 (16)	19.79***
Pregnant as a teen %(n)	14.6 (47)	24.4 (11)	13.8 (4)	2.95
Living in poverty %(n)	13.7 (44)	26.7 (12)	31.0 (9)	9.66**
Secondary education or less %(n)	28.0 (90)	57.8 (26)	58.6 (17)	24.35**
Higher crime rate residence %(n)	26.2 (84)	55.6 (25)	44.8 (13)	18.82***
Number of SES risk factors (0–5), mean (SD)	1.1 (1.7)	2.2 (1.8)	2.0 (1.5)	11.19**
Trauma and PTSD				
	% (n) or mean (SD)			
Sum of trauma types (0–29), mean(SD)	3.5 (3.2)	5.7 (3.6)	7.9 (5.7)	26.16***
Lifetime PTSD diagnosis %(n)	21.8 (70)	44.4 (20)	58.6 (17)	26.00***
Current PTSD diagnosis %(n)	7.2 (23)	11.1 (5)	31.0 (9)	18.03***
Lifetime PTSD symptom count, mean(SD)	2.9 (4.4)	5.0 (4.9)	7.8 (5.8)	17.58***
Current PTSD symptom count, mean(SD)	1.5 (2.9)	3.0 (3.5)	4.7 (8.8)	16.65***
Cortisol levels (ug/dL)				
	mean (SD)			
Morning, mean(SD), n=392	.41 (.23) n=318	.42 (.32) n=45	.38 (.24) n=29	.33 [^] .74 [^] (log)
Late afternoon, mean(SD), n=387	.10 (.09) n=313	.12 (.13) n=45	.21 (.26) n=29	12.78*** 4.13 (log) *
Bedtime, mean(SD), n=394	.08 (.10) n=321	.08 (.08) n=44	.20 (.27) n=29	13.31*** 5.11**

*
p<.05,**
p<.01,***
p<.001,[^]
F is result using natural units (ug/dL), and second is results are from ANOVA using log-transformed values.