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Psychophysiology and posttraumatic stress disorder symptom profile in pregnant African-American women with trauma exposure

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Abstract

While female sex is a robust risk factor for posttraumatic stress disorder (PTSD), pregnant women are an understudied population in regards to PTSD symptom expression profiles. Because circulating hormones during pregnancy affect emotionality, we assessed whether pregnant women would have increased expression of the intermediate phenotypes of hyperarousal and fear-potentiated startle (FPS) compared to non-pregnant women. We examined PTSD symptom profiles in pregnant ($n=207$) and non-pregnant women ($n=370$). In a second study, FPS responses were assessed in 15 pregnant and 24 non-pregnant women. All participants were recruited from the obstetrics and gynecology clinic at a public hospital serving a primarily African-American,

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low socioeconomic status, inner-city population. Our results indicate that overall PTSD symptoms were not different between the groups of women. However, pregnant women reported being more hypervigilant ($p=0.036$) than non-pregnant women. In addition, pregnant women showed increased FPS to a safety signal compared to non-pregnant women ($p=0.024$). FPS to a safety signal in pregnant women was significantly correlated with PTSD hyperarousal symptoms ($r=0.731$, $p<0.001$). Furthermore, discrimination between danger and safety signals was present in non-pregnant women ($p=0.008$), but not in pregnant women ($p=0.895$). Together, these data suggest that pregnant women show clinical and psychophysiological hyperarousal compared to non-pregnant women, and support screening for PTSD and assessment of PTSD risk in pregnant women.

Keywords

PTSD; Pregnancy; Women; Psychophysiology; Hyperarousal; Startle

Introduction

Epidemiological studies from the last decade illustrate that female sex is a risk factor for psychopathology, including depression (Weissman and Olfson 1995) and posttraumatic stress disorder (PTSD) (Bromet et al. 1998). More recently, an array of studies have shown that women throughout the world are at increased risk for PTSD compared to men (Dell’Osso et al. 2013; Landolt et al. 2013), across military (Kline et al. 2013), civilian (Steven Betts et al. 2013), adolescent (Landolt et al. 2013), and geriatric cohorts (Zhang et al. 2012). One group of women that has been underrepresented in the study of PTSD includes those who are pregnant. Given the increased risk for preterm birth in pregnant women with PTSD (Yonkers et al. 2014) and the cross-generational transmission of PTSD risk and neuroendocrine dysregulation observed in infants born to women traumatized during gestation (Brand et al. 2006; Brennan et al. 2008; Yehuda et al. 2005), research on the association between pregnancy and PTSD can provide insight into treatments of PTSD tailored specifically for pregnant women. While a handful of studies describe high rates of trauma exposure during pregnancy (Dailey et al. 2011; Seng et al. 2009), only a few existing studies describe rates of PTSD (Seng et al. 2009) and PTSD symptoms in pregnant women (Seng et al. 2010; Smith et al. 2006). Epidemiological studies indicate that rates of PTSD are 4–5 % higher in pregnant compared to non-pregnant women (Seng et al. 2010). The results from the two studies assessing how PTSD symptom profile is altered in pregnancy are equivocal, as one concluded that re-experiencing symptoms were decreased in pregnant compared to non-pregnant women (Smith et al. 2006) and the other described a higher rate of detachment, loss of interest, anger, difficulty sleeping, and nightmares in pregnant compared to non-pregnant women (Seng et al. 2010). The discordance between these studies could be due to the fact that the data for pregnant and non-pregnant women were collected from two separate and distinct cohorts of women (Seng et al. 2010; Smith et al. 2006). A psychophysiological biomarker that has been associated with PTSD symptoms can provide information on potential neurobiological bases for altered PTSD symptoms in pregnancy.

One psychophysiological hallmark of PTSD that has not yet been described in pregnant women is an exaggerated fear response and impaired inhibition of conditioned fear (Jovanovic and Ressler 2010). Augmented fear-potentiated startle (FPS) to a safety signal is a robust biomarker for PTSD in both military and civilian populations (Jovanovic et al. 2012; Lissek et al. 2005). FPS is measured by the relative increase in the acoustic startle reflex in the presence of conditioned stimuli that have been paired with aversive unconditioned stimuli (Jovanovic et al. 2012). Differential fear conditioning involves two distinct cues: the reinforced conditioned stimulus (CS+, also referred to as the danger signal) and a non-reinforced conditioned stimulus (CS-, also referred to as the safety signal). It has been proposed that the inability to discriminate between danger and safety signals in PTSD arises from an over-generalization of stimuli that can manifest as increased arousal (Jovanovic et al. 2012). This notion is supported by the fact that FPS to a safety signal is positively associated with hyperarousal symptoms in individuals with PTSD (Jovanovic et al. 2012).

Importantly, steroid hormones that are critical for the regulation of behavior and physiology in females (McEwen 2002, 2008; Michopoulos and Wilson 2011; Toufexis et al. 2004) increase during pregnancy (Soldin et al. 2005) and modulate FPS. Low estradiol (E2) levels in women are associated with impaired inhibition of fear (Glover et al. 2013) and decreased extinction of fear (Glover et al. 2012). Activity of the limbic-hypothalamic-pituitary-adrenal (LHPA) axis via cortisol and corticotropin-releasing hormone (CRH) is also capable of modulating fear responses (Keen-Rhinehart et al. 2009; Sanchez et al. 2005) such that exacerbated startle response in individuals with PTSD is associated with increased levels of adrenocorticotrophic hormone (ACTH) and cortisol (Grillon et al. 2006; Jovanovic et al. 2010b). Thus, the increased levels in estradiol and cortisol over the course of pregnancy (Soldin et al. 2005) suggest that changes in hormone levels could influence arousal and FPS in pregnant women. However, the directionality of this change remains uncertain as E2 acts to attenuate FPS and cortisol acts to increase FPS. Thus, we assessed whether pregnant women would show altered levels of hyperarousal and FPS compared to non-pregnant women in two separate studies. We hypothesized that pregnancy would be associated with increased hypervigilance manifested in clinical symptom severity and higher startle to safety signals.

Methods

Subjects

All study participants were women recruited from the outpatient obstetrics and gynecology (OB/GYN) clinic at Grady Memorial Hospital in Atlanta, GA, serving a primarily African-American, low socioeconomic status (SES), innercity population (Gillespie et al. 2009). Women were approached randomly while in primary care and OB/GYN clinics by a member of the research team and solicited for study participation. Potential subjects were informed that the study examined childhood and adulthood trauma exposure (Gillespie et al. 2009). Pregnant women in all stages of pregnancy were included in the current study as well as premenopausal non-pregnant women. Both groups of women were recruited in the same manner. Individuals were English-speaking and between the ages of 18 and 50 years who

provided written informed consent and recruited as previously described (Gillespie et al. 2009). Exclusion criteria for the current study included mental retardation and active psychosis. All study procedures were reviewed and approved by the Emory Institutional Review Board and the Grady Hospital Research Oversight Committee.

Study one

The first study included a total of 577 participants to assess whether PTSD symptoms were different between pregnant ($n=207$) and non-pregnant ($n=370$) women. Pregnancy status was assessed by self-report via a Demographics Form (Gillespie et al. 2009). Lifetime history of traumatic event exposure was measured using the 14-item Traumatic Events Inventory (TEI) (Schwartz et al. 2005), and childhood trauma exposure was assessed by the 28-item Childhood Trauma Questionnaire (CTQ) (Bernstein et al. 1997). The Beck Depression Inventory (BDI) was given to assess the presence of current depressive symptoms (Beck et al. 1961). PTSD symptoms were assessed using the previously validated PTSD Symptom Scale (PSS) (Foa et al. 1993). The PSS is a psychometrically valid 17-item self-report scale assessing PTSD symptoms over the past 2 weeks (Foa and Tolin 2000; Schwartz et al. 2005). Consistent with previous convention, we summed the PSS frequency items to obtain a continuous measure of PTSD symptom severity (Gillespie et al. 2009). Similarly, we computed continuous measures for sub-clusters of symptom severity, including re-experiencing, avoidance, and hyperarousal symptom clusters. Finally, we assessed hypervigilance by looking at the severity of the single item of being “overly alert.”

Study two

A sample of 39 participants from study one (14 pregnant and 25 non-pregnant women; confirmed by pregnancy test) matched on age, TEI, CTQ, BDI, and PSS scores, were tested using the Fear-Potentiated Startle Paradigm (Glover et al. 2011) to assess the effects of pregnancy on neuropsychophysiology. PTSD diagnosis status was determined using DSM-IV criteria based on the PSS, which has shown high validity with the Clinician Administered PTSD Scale (CAPS). Women were excluded if they were not able to detect frequencies ranging from 250 to 4,000 Hz and tones at 30 dB as measured using an audiometer (Grason-Stadler, Model GS1710). Additional exclusion criteria included positive urine toxicology for cocaine, active psychosis, head injury with loss of consciousness, or neurological disorders.

The Fear-Potentiated Startle paradigm consisted of an initial habituation phase wherein conditioned stimuli (CS) were presented without any reinforcement (Fig. 1) (Glover et al. 2011; Norrholm et al. 2011). The acquisition phase consisted of three blocks with four trials of each type of CS (reinforced conditioned stimulus, CS+; non-reinforced conditioned stimulus, CS-; noise probe alone, NA) for 12 trials per block and a total of 36 trials. Both CSs were colored shapes (i.e., blue square, purple triangle) presented on a computer monitor for 6 s each and counterbalanced across subjects. The unconditioned stimulus (US; aversive stimulus) was a 250-msec air blast of 140-psi intensity to the larynx that has been shown in our previous studies to produce a robust fear-potentiated startle response (Glover et al. 2011; Norrholm et al. 2011). The air blast was delivered from a compressed air tank via a polyethylene tub and controlled by a solenoid switch. The intertrial intervals throughout the acquisition phase were randomized to be between nine and 22 s in duration.

Startle response data were acquired using the electromyography (EMG) module of the BIOPAC MP150 for Windows (Biopac Systems, Goleta, California). The acquired data were filtered, rectified, and smoothed using the MindWare software suite (MindWare Technologies, Gahanna, Ohio) and exported for statistical analyses. The eye-blink component of the acoustic startle response was measured by EMG recordings of the right orbicularis oculi muscle with two 5-mm Ag/AgCl electrodes filled with electrolyte gel as previously described (Glover et al. 2011; Jovanovic et al. 2010a). One electrode was positioned 1 cm below the pupil of the right eye, and the other was placed 1 cm below the lateral canthus. A ground electrode was placed on the mastoid bone. Impedance levels were less than 6 kiloOhms for each participant. The EMG signal was sampled at a frequency of 1 kHz and filtered with low- and high-frequency cutoffs at 28 and 500 Hz, respectively. The maximum amplitude of the eye-blink muscle contraction 20 to 200 msec after presentation of the startle probe was used as a measure of the acoustic startle response. The startle probe was a 108-dB [A] SPL, 40-msec burst of broadband noise with near instantaneous rise time, delivered binaurally through headphones. As previously described (Jovanovic et al. 2012), trial-by-trial US expectancy and contingency awareness was measured during fear conditioning via a response keypad unit (SuperLab, Cedrus Corp., San Pedro, CA). Subjects were instructed to respond on each CS trial by pressing one of three buttons to indicate whether they expected the airblast (+button), did not expect the airblast (–button), or were uncertain (0 button).

All women were informed about the startle paradigm and that it would entail hearing loud noises and getting a blast of air directed at their neck, and were told they were free to stop participation at any point during the session. The participants were seated in a chair in a sound-attenuated booth with a computer monitor 2 ft in front of them. Women were fitted with the airblast delivery vest and EMG electrodes were placed under their eye and the headphones were placed on their ears. The startle session lasted approximately 30 min. There were no adverse reactions to the paradigm, and all women completed the fear conditioning session.

Statistical analyses

Chi-square analysis was used to assess differences between non-pregnant and pregnant women on categorical variables and analyses of variance (ANOVA) for continuous variables in both studies. Potentiation of the startle reflex was assessed by comparing average startle magnitude on the CS+ trials to the average startle magnitude to the NA trials using repeated-measures ANOVA (RM-ANOVA) with Trial Type as the within-subjects factor and Pregnancy status as a between-subjects factor. PTSD diagnosis (Yes, No) was also included as a between-subjects factor given that PTSD has been associated with dysregulated FPS (Jovanovic et al. 2010a). Discrimination between danger signals (CS+) and safety signals (CS–) was assessed using an FPS Difference Score, by subtracting startle magnitude on the CS trials to startle magnitude on the NA trials. This Difference Score controlled for individual variation in startle magnitude. Bivariate correlation was used to assess association between FPS Difference Scores to each CS and hyperarousal symptoms in study two. Statistical values with a $p < 0.05$ were considered significant. Partial eta squared measures of effect size are included given the small sample size of the FPS analyses.

Results

Study one

Demographic characteristics—Pregnant and non-pregnant women in the larger sample did not differ by race ($p=0.56$; Table 1). However, non-pregnant women in the sample were significantly older than the pregnant group [$F(1,576)=85.2$, $p<0.001$; Table 1]. For this reason, all subsequent analyses for study one controlled for age.

Trauma exposure—Overall trauma exposure as determined by the TEI was not significantly different between pregnant and non-pregnant women [$F(1,576)=0.27$, $p=0.60$]. Pregnant women experienced a total of 2.86 ± 0.16 criterion A trauma types (APA 2000) and non-pregnant women experienced a total of 2.73 ± 0.11 criterion A trauma types (Table 1). Furthermore, childhood trauma exposure was not different between pregnant and non-pregnant women [$F(1,576)=0.51$, $p=0.82$; Table 1].

PTSD and depressive symptoms—There was no difference between pregnant and non-pregnant women in the categorical diagnosis of PTSD using the PSS ($\chi^2<0.001$; $p=0.99$; $n=577$). The percentage of pregnant women with PTSD was 29.9 and 30.0 % in non-pregnant women (Table 1). Overall PTSD symptoms as well as the subgroups of avoidance and hyper-arousal symptoms were not different between the two groups of women (all $p>0.05$; Table 1). The intrusive symptom cluster did trend towards significance with pregnant women reporting greater intrusive and re-experiencing symptoms than non-pregnant women [$F(1,576)=3.39$, $p=0.07$; Table 1]. Furthermore, as predicted, pregnant women reported being significantly more overly alert [$F(1,576)=4.42$, $p=0.036$] than non-pregnant women (Table 1). Finally, depressive symptom levels based on the BDI were not different between pregnant and non-pregnant women [$F(1,572)=1.28$, $p=0.26$; Table 1].

As stated above, these analyses controlled for age as pregnant women were significantly younger than non-pregnant women, and age was positively correlated with hyperarousal symptoms ($r=0.13$; $p=0.003$). In order to test the independent contributions of age and pregnancy on being overly alert, we performed a stepwise regression analysis with age entered at step one and pregnancy in the next step. Pregnancy was still independently predictive of these PTSD symptoms ($F=4.95$, $p<0.05$), with age accounting for only 0.6 % of the variance in hypervigilance.

Study two

Demographic and clinical characteristics—Pregnant and non-pregnant participants of the FPS experiment were matched for age, total trauma experienced as measured by the TEI, total CTQ score, total BDI score, and total PSS score (all $p>0.05$; Table 2).

Fear-potentiated startle response—In order to examine whether pregnancy affected fear potentiation of the startle reflex, we compared startle responses to noise alone (NA) trials to trials paired with the airblast (CS+) during the late phase of fear acquisition (blocks 2 and 3), as in our previous studies (Glover et al. 2011; Norrholm et al. 2011). An RM-ANOVA assessing the effects of Trial Type (CS+ vs. NA), Pregnancy status (Yes, No), and

PTSD diagnosis (Yes, No) revealed a significant effect of Trial Type on startle magnitude [$F(1,35)=21.41, p<0.0001, n^2=0.38$] but no interaction effects with Pregnancy or PTSD (both $p>0.05, n^2=0.06$ and $n^2=0.03$, respectively). These data suggest that all participants showed similar increases in startle response to the danger cue compared to baseline (see Fig. 2a).

We next examined discrimination between danger and safety cues using an RM-ANOVA of Trial Type (CS+ vs. CS-) by Pregnancy and by PTSD diagnosis, with FPS Difference Score as the dependent measure. While there were no significant main effects of Trial Type, Pregnancy status, or PTSD diagnosis (all $p>0.05$), there was a significant interaction between Trial Type and Pregnancy status on FPS [$F(1,35)=8.14, p=0.007, n^2=0.19$]. Separate analyses of the two groups of women revealed that pregnant women did not show discrimination between danger and safety signals [$F(1,14)=0.02, p=0.89, n^2=0.002$; Fig. 2b], while non-pregnant women showed higher FPS to the danger signal than the safety signal [$F(1,23)=8.38, p=0.008, n^2=0.27$; Fig. 2b]. The lack of discrimination in the pregnant women was due to an increase in FPS to the safety signal in pregnant women in comparison to non-pregnant women [$F(1,35)=5.56, p=0.024, n^2=0.14$; Fig. 2b], whereas there was no difference between the groups regarding FPS to the danger signal [$F(1,35)=2.29, p=0.14, n^2=0.06$; Fig. 2b]. Bivariate correlations within each group revealed that FPS to the safety signal was positively associated with hyperarousal symptoms of PTSD in pregnant women ($r=0.73, p=0.002$), but not in non-pregnant women ($r=0.09, p=0.69$, Fig. 3). In order to examine the effect of depressive symptoms during pregnancy on FPS, we repeated the above analysis while covarying for BDI score. PTSD hyperarousal was still significantly correlated with FPS to the safety signal ($r=0.76, p=0.003$), while depression was not ($r=0.29, p=0.32$).

Contingency awareness—Response pad data from 35 participants (14 pregnant and 21 non-pregnant) were collected, with 4 non-pregnant participants' data missing due to computer error. We repeated the same analysis as above, but using the response pad data on US expectancy from blocks 2 and 3 of the conditioning session as the dependent variable. We found a significant main effect of CS Type [$F(1,31)=50.78, p<0.001, n^2=0.62$], with the participants reporting higher US expectancy on the CS+ trials than the CS- trials. There were no interaction effects with either Pregnancy or PTSD diagnosis, indicating that both pregnant and non-pregnant women showed discrimination on a cognitive level.

Discussion

The results from the current studies indicate that pregnant women reported being significantly more overly alert and exhibited increased FPS to a safety signal compared to non-pregnant women. Interestingly, FPS to a safety signal was significantly correlated with PTSD hyperarousal symptoms only in pregnant women and not in non-pregnant women. Finally, pregnant women did not show startle discrimination between danger and safety signals whereas non-pregnant women showed higher startle to the danger cue relative to the safety cue. Importantly, both pregnant and non-pregnant showed evidence of learning of reinforcement contingencies, based on the response keypad data, demonstrating that the lack of discrimination in the pregnant women was not due to an impaired ability to learn the association between the cue and the air blast. To our knowledge, this is the first examination

of PTSD symptom profile of pregnant and non-pregnant women from the same population, and the first report of increased hypervigilance and FPS in pregnant women.

The incidence of PTSD in the larger sample was not different between pregnant and non-pregnant women in the current study (~30 %), but overall was significantly higher than previous reports of PTSD in pregnant women (~8 %) (Ayers and Pickering 2001; Loveland Cook 2004; Seng et al. 2010) that described overall lower rates of trauma exposure between 3.5 and 16 % (Morland et al. 2007; Seng et al. 2010; Smith et al. 2006). The high PTSD incidence in the current study parallels the higher rates of trauma exposure described in the primary care population at Grady Memorial Hospital in Atlanta, GA (Gillespie et al. 2009). Overall PTSD symptoms were not different between pregnant and non-pregnant women of reproductive age, but pregnant women reported being more overly alert than non-pregnant women. It is important to note that age was positively associated with hyperarousal symptoms, and that the pregnant women reported higher hypervigilance despite being significantly younger than non-pregnant women. The specificity of the findings in the clinical sample corroborates the clinical significance of impaired regulation of fear-potentiated startle in response to safety signals.

Impaired inhibition of conditioned fear appears to be a psychophysiological hallmark of PTSD (Jovanovic and Ressler 2010). Specifically, increased FPS to a safety signal is a robust biomarker for anxiety disorders (Lissek et al. 2005), including PTSD (Jovanovic et al. 2012; Lissek et al. 2005), and is associated with severity of current PTSD symptoms (Jovanovic et al. 2009). In individuals with PTSD, FPS to a safety signal is positively associated with hyperarousal symptoms (Jovanovic et al. 2010b), a finding we also report in the current study in pregnant women only. Additionally, pregnancy in the current study was associated with an inability to discriminate between danger and safety signals, while such differential responses were observed in non-pregnant women. Poor discrimination between conditioned stimuli may be due in part to over-generalization of the CS+ to other similar cues, which has been found to be associated with fear-related pathophysiology (Lissek et al. 2010). Increased startle to both negative and positive images and lack of discrimination between stimuli has previously been described in pregnant women (Hellgren et al. 2012). Taken together, our data suggest that pregnancy may be associated with increased arousal and hypervigilance, similar to what has been described in individuals with PTSD.

The increase in FPS and hyperarousal, and the positive relationship between the two in pregnant women, suggests that biological changes during pregnancy may be responsible for altering arousal in women. This notion is supported by findings indicating that increased startle to visual stimuli during late pregnancy normalizes post-partum (Hellgren et al. 2012). Pregnancy is characterized by neuroendocrine changes that could influence the expression of hyperarousal and fear. Concentrations of ovarian hormones increase during pregnancy (Soldin et al. 2005), and are capable of reducing arousal state and fear (Glover et al. 2013; Toufexis et al. 2004). Estradiol (E2) attenuates the expression of fear (Glover et al. 2013) and decreases FPS during extinction of fear (Glover et al. 2012). Progesterone via its metabolite allopregnanolone attenuates CRH-enhanced startle but has no effect on FPS in female rats (Toufexis et al. 2004). Furthermore, increased activity of the LHPA axis during pregnancy could also contribute to the observed increase in arousal in pregnant women.

Studies in rodents, non-human primates, and humans indicate that increased cortisol and LHPA activity are associated with increased startle (Keen-Rhinehart et al. 2009; Sanchez et al. 2005). Additionally, increased levels of ACTH and cortisol are associated with exacerbated startle response in individuals with PTSD (Grillon et al. 2006; Jovanovic et al. 2010b). Our finding that arousal was exacerbated in pregnancy, and not decreased, suggests that increased ACTH and cortisol during pregnancy (Mastorakos and Ilias 2003; Soldin et al. 2005), and not increased E2 levels, are associated with this hypervigilance. However, because E2 is capable of increasing CRH (Roy et al. 1999) and basal cortisol levels in females (Burlison et al. 1998; Gudmundsson et al. 1999), we cannot rule out the possibility that an interaction between gonadal and stress axes during pregnancy acts to modulate arousal state in women. Future studies that sample hormone levels along with startle responses during gestation are necessary to determine exactly how E2 and cortisol levels during pregnancy are associated with FPS and hyperarousal.

Our findings of increased arousal do not corroborate previous reports of altered PTSD symptoms in pregnant women. However, this is the first time in which changes in hyperarousal have been described in pregnancy, as results from the two large epidemiological studies assessing PTSD symptom profile in pregnant women indicate changes in re-experiencing and avoidance symptoms (Seng et al. 2010; Smith et al. 2006). While re-experiencing symptoms were decreased in pregnant compared to non-pregnant women in one study (Smith et al. 2006), rates of detachment, loss of interest, anger, difficulty sleeping, and nightmares were increased in pregnant compared to non-pregnant women in the second study (Seng et al. 2010). Our own data indicated on a trend level that re-experiencing symptoms might indeed be greater in pregnant women, but as perinatal PTSD research remains in its infancy, more robust investigations are necessary to elucidate the specificity of symptom changes over the course of pregnancy. Overall, past studies are limited as the comparisons made between pregnant and non-pregnant women from different study cohorts (Smith et al. 2006). The current study compared pregnant and non-pregnant women that were drawn from the same sample population, with similar rates of trauma exposure. Thus, the current study does not suffer from potential misclassification and sample bias that previous studies may have included (Smith et al. 2006).

Differences in PTSD symptom profiles among pregnant women described in previous studies have been attributed to an array of possible factors beyond the neuroendocrine changes associated with pregnancy (Seng et al. 2010). Activity of the autonomic nervous system is altered during pregnancy (Kuo et al. 2000), leading to changes in heart and respiration rate that could influence the reporting of increased arousal in pregnant women in the current study. Pregnancy could also alter the reporting of PTSD symptoms on research instruments (Seng et al. 2010) similar to what has been described with depressive symptoms (Kilpatrick et al. 2003). Alterations in symptoms during pregnancy could indeed be interpreted as leading to a lack of validity in the use of measures to assess for psychopathology in pregnancy (Seng et al. 2010). However, it becomes more prudent to take the perspective that differences in symptom levels reported during pregnancy are meaningful because they provide us with a natural occurrence wherein changes in physiology due to pregnancy alter behavior. Indeed, hyperarousal during pregnancy is congruent with the notion that emotional sensitivity increases during pregnancy and serves as an evolutionary

advantage to promote the survival of the fetus and mother (Pearson et al. 2009). More specifically, hypervigilance in a dangerous environment is likely highly adaptive; given that the participants in the current study were recruited from an inner-city population with high rates of violence and trauma exposure (Gillespie et al. 2009), it is possible that the deficient responses to safety signals and the associated over-generalization of danger signals is adaptive during pregnancy. On the other hand, such over-generalization can potentially increase risk for psychopathology in pregnant women (Lissek et al. 2013), which may continue post-partum.

Psychopathology in pregnancy, including PTSD and depression, can lead to transgenerational effects on offspring physiology and behavior (Brand et al. 2006; Brennan et al. 2008; Yehuda et al. 2005). Maternal depression during pregnancy is not only associated with increased cortisol levels in mothers but also with increased cortisol and LHPA axis reactivity in infants (Brennan et al. 2008). Maternal cortisol levels have also been linked to increased amygdala volumes and affective problems in children (Buss et al. 2012). PTSD in women exposed to trauma during pregnancy has been linked to a dysregulation of the LHPA axis that manifests as attenuated levels of basal cortisol levels (Brand et al. 2006). Importantly, morning cortisol in mothers with PTSD is inversely related to infant distress to novelty (Brand et al. 2006). Infants of mothers with PTSD show overall more levels of distress to novelty and have decreased cortisol levels compared to infants of mothers exposed to trauma during pregnancy who did not develop PTSD (Yehuda et al. 2005). Furthermore, infant cortisol levels have been associated with negative affect in offspring later on as toddlers (Huot et al. 2004). Taken together, these data indicate that psychopathology during pregnancy can affect offspring biology and increase offspring risk for PTSD and depression. The current study may point to another mechanism of such transgenerational effects whereby maternal hypervigilance and over-generalization of fear responses is transferred to the offspring. Recent rodent data suggest that fear-conditioned behavior can be epigenetically transferred from parents to offspring (Dias and Ressler 2014). Further studies are necessary to determine whether increased cortisol and hypervigilance in pregnancy interact to facilitate epigenetic changes that are expressed in offspring of mothers.

In summary, the current cross-sectional data from a highly traumatized population indicate that pregnant women show symptomatic and psychophysiological hyperarousal. Limitations of the current study include the fact that neuroendocrine markers whose levels change with pregnancy were not measured, as well as trimester status of pregnancy and use of birth control in non-pregnant women were unknown. Additionally, our inner-city hospital sample is not a population-based sample, and thus selection biases could be present in the small subset of individuals who selected to participate in the current study. Furthermore, while our data showing increased FPS in pregnant women is novel, they should be considered preliminary due to our small sample size. However, the large effect sizes suggest that pregnancy accounts for a moderate to large amount of variance in fear inhibition.

In future studies, a repeated-measures study in women before and after pregnancy will be necessary to definitively assess how PTSD symptom profile and fear dysregulation is altered by pregnancy. Data from a longitudinal startle study comparing pregnancy to post-partum suggests that fear physiology may normalize after pregnancy (Hellgren et al. 2012). Lastly,

the current data taken together with data describing increased risk for trauma exposure (Dailey et al. 2011; Gazmararian et al. 2000) and adverse perinatal health outcomes (Matthews and MacDorman 2007) in pregnant, low SES African-American women, indicate that PTSD symptom presentation can be altered by pregnancy and that treatment of PTSD in pregnant women could be tailored to target attenuating arousal and startle, as well as focusing on signal discrimination. Similarly, these data suggest that increased screening for PTSD and assessment of PTSD risk in pregnant women could be important for identifying women at risk for adverse perinatal health outcomes (Yonkers et al. 2014). Further studies are necessary to assess how increased hypervigilance during pregnancy influences birth outcomes, parenting behavior, and behavioral and physiological development of the offspring.

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FEAR ACQUISITION

Fig. 1. Diagram of the fear-potentiated startle (FPS) experiment. CS+ reinforced conditioned stimulus (danger signal) and CS- non-reinforced conditioned stimulus (safety signal)

Fig. 2.

a Mean $\pm$ SEM startle magnitude in pregnant and non-pregnant women to the noise alone (NA, baseline startle) and CS+ (danger signal). An *asterisk* (*) denotes significant potentiation of startle to the CS+ compared to NA (both groups $p<0.001$). **b** Mean $\pm$ SEM fear-potentiated startle in pregnant and non-pregnant women to the CS+ (danger signal) and CS- (safety signal). Fear-potentiated startle was measured using a Difference Score of startle magnitude to each CS minus startle magnitude to noise alone (NA) startle. A *pound sign* (#) denotes significantly greater FPS to the CS- (safety signal) in pregnant compared to non-pregnant women ($p=0.024$). An *asterisk* (*) denotes significant discrimination between the CS+ and CS- in non-pregnant women ($p=0.008$) whereas pregnant women do not discriminate. CS conditioned stimulus, FPS fear-potentiated startle, NA noise alone

Fig. 3. Fear-potentiated startle to the CS- (safety signal) was positively associated with hyperarousal symptoms in pregnant women ($r=0.73$, $p=0.002$), but not in non-pregnant women ($r=0.09$, $p=0.69$)

Table 1

Demographic and clinical characteristics shown as the mean±SEM in epidemiological assessment of PTSD symptoms in pregnant and non-pregnant women

Demographic characteristics	Pregnant (n=207)	Non-pregnant (n=370)	P value
Age (years)	26.1 ±0.60	33.1±0.45	<0.001 **
Race (no./total no.)			0.56
African-American	192 (92.7 %)	350 (94.6 %)	
Hispanic/Latino	2 (0.9 %)	2 (0.5 %)	
White	3 (1.4 %)	3 (0.8 %)	
Mixed	5 (2.4 %)	4 (1.1 %)	
Other	5 (2.4 %)	5 (1.4 %)	
Clinical characteristics			
Trauma exposure (TEI)	2.86±0.16	2.73±0.11	0.60
CTQ childhood trauma total	41.8±0.97	41.4± 1.32	0.82
PTSD diagnosis (no./total no.)			0.99
Yes	62 (30.0 %)	111 (30.0 %)	
No	145 (70.0 %)	259 (70.0 %)	
Total PTSD symptoms (PSS)	13.8±0.90	12.6±0.66	0.28
Re-experiencing (PSS)	3.53±0.28	2.88±0.20	0.07
Avoidance (PSS)	5.37±0.41	5.27±0.30	0.84
Hyperarousal (PSS)	4.91±0.31	4.42±0.23	0.22
Overly alert (PSS, item 15)	1.46±0.10	1.19±0.07	<0.05 *
BDI total symptoms	14.6±0.64	15.8±0.86	0.26

Asterisks denote significant differences in age (**) and in alertness (*; $p=0.036$) between pregnant and non-pregnant women

Table 2

Demographic characteristics shown as the mean±SEM of pregnant and non-pregnant women that participated in the fear-potentiated startle (FSP) experiment

	Pregnant (n=15)	Non-pregnant (n=24)	p value
Age	24.8± 1.12	25.7±0.86	0.54
TEI total experienced	2.60±0.69	3.14±0.54	0.54
CTQ total score	43.8±5.51	38.1±3.38	0.35
BDI total score	18.2±3.29	14.0±1.76	0.23
PSS total score	15.6±3.64	12.0±1.96	0.34

Pregnant and non-pregnant women did not differ on any measures assessed (all $p>0.05$)