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Perinatal depression, adverse life events and HPA axis response to cold pressor stress in Latinas: An exploratory study

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Abstract

Background—Latinas are disproportionately affected by perinatal depression (PND) as well as by adverse life events (ALEs), an independent predictor of PND. Dysregulation of the hypothalamic-adrenal-pituitary (HPA) axis has been seen both in women with PND and with a history of ALEs in non-Latinas. Though some evidence suggests that HPA axis dysregulation may mediate the link between ALEs and PND, this has received little attention and there are no studies that have examined these pathways in Latinas. The primary aim of the present study was to explore, in a Latina sample, associations between ALEs, PND, and HPA axis stress reactivity to a physical stressor—the cold pressor test (CPT). The secondary aim was to explore whether HPA axis reactivity and PND were associated with pain sensitivity to the CPT.

Methods—Thirty-four Latinas were enrolled in their third trimester of pregnancy and interviewed at 4 and 8 weeks postpartum. Depression status was determined using the Edinburgh Postnatal Depression Scale (EPDS-10). At 8 weeks postpartum, 27 women underwent laboratory-induced pain testing using the cold pressor test (CPT). Plasma adrenocorticotrophic hormone (ACTH) and cortisol (CORT) were sampled pre- and post-CPT to generate a stress reactivity score (post-pre). Pain sensitivity and ALEs were also assessed.

Results—At enrollment, 26% of women were depressed and 18% were depressed at 8 weeks postpartum. Forty-eight percent reported at least one childhood ALE. There was a significant and positive association between any childhood ALE and prenatal depression scores ($p = 0.025$).

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Infant-related ALEs were significantly associated with greater ACTH reactivity to the CPT ($p = 0.030$). Women with a history of any childhood ALE exhibited a blunted CORT response to the CPT ($p = 0.045$). Women with a history of PND at 4 weeks had greater ACTH stress reactivity to the CPT ($p = 0.027$). No significant effects of PND were seen for pain sensitivity measures in response to the CPT, though there was a positive and significant correlation between pain tolerance and CORT response to the CPT in the whole sample.

Conclusions—Given the associations between ALEs and PND and their individual effect on HPA axis stress reactivity, future studies on perinatal depression should include a larger sample of Latinas to test mediating effects of HPA axis reactivity on associations between ALEs and PND.

Keywords

Latina; adverse life events; HPA axis; perinatal depression; pain sensitivity

Introduction

Latinos are the prevailing ethnic minority group in the United States (Census, 2013). With the highest fertility rate in the U.S. (Passel, 2013), Latinas accounted for 24% of live births in 2010, with 56% of those being from immigrant women (Livingston & Cohn, 2012). Given this population's rate of growth, research regarding prenatal and postpartum depression (PPD), also referred to as perinatal depression, is essential (Lara-Cinisomo, Wisner, & Meltzer-Brody, 2015). Latinas suffer high rates of perinatal depression compared to non-Latinas yet there has been little research designed to understand the risk factors or pathophysiology that might contribute to this increased risk.

Perinatal depression (PND) is characterized as a major depressive episode occurring in pregnancy or in the first postpartum year (American Psychiatric Association, 2013; Gavin et al., 2005). While PND is seen in up to 12–19% of women in the general population (Gavin et al., 2005), the occurrence of PND in Latinas living in the US has been estimated at 30–53% (Ceballos, Wallace, & Goodwin, 2016; Kieffer et al., 2013; Kuo et al., 2004; Lucero, Beckstrand, Callister, & Sanchez Birkhead, 2012; Mukherjee, Trepka, Pierre-Victor, Bahelah, & Avent, 2016; Zayas, Jankowski, & McKee, 2003). Although the causes of perinatal depression remain elusive, adverse life events (ALEs), such as childhood abuse and intimate partner violence, are potent risk factors for perinatal depression (Alvarez-Segura et al., 2014; Buist & Janson, 2001; Faisal-Cury, Menezes, d'Oliveira, Schraiber, & Lopes, 2013; Meltzer-Brody et al., 2013; Plaza et al., 2012; Rodríguez et al., 2010).

There is growing evidence that exposure to ALEs, including those in early life, can lead to long-term dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis response to stress (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Klaassens et al., 2009; Shea, Walsh, MacMillan, & Steiner, 2005), and this dysregulation may manifest as either a blunted or exaggerated stress response (McEwen, 1998). Briefly, in response to a perceived stressor, the hypothalamus releases corticotrophic-releasing hormone (CRH), which then triggers the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH) into the blood stream (Tsigos & Chrousos, 2002). The adrenal cortex is subsequently stimulated by ACTH to produce and release cortisol. Activation of the HPA axis is tempered by a negative feedback

loop, which involves cortisol suppressing the further release of CRH and ACTH by binding to glucocorticoid receptors in the hypothalamus and pituitary gland (Blume, Douglas, & Evans, 2011). This negative feedback loop reestablishes homeostasis to ultimately regulate cortisol release in response to stress.

Dysregulation in the HPA axis has been implicated in PND (Bloch, Daly, & Rubinow, 2003; E. Q. Cox et al., 2015; de Rezende et al., 2016; Glynn, Davis, & Sandman, 2013; Groer & Morgan, 2007; Magiakou et al., 1996; Parry et al., 2003; Yim, Tanner Stapleton, Guardino, Hahn-Holbrook, & Dunkel Schetter, 2015). For example, Jolley et al. showed that at 6 and 12 weeks postpartum, women with depression had higher ACTH levels and lower CORT levels compared to nondepressed postpartum women during physical stress testing (Jolley, Elmore, Barnard, & Carr, 2007). Although the research on the association of ALEs to HPA axis function during the perinatal period is extremely limited to date, one study found that perinatal women with histories of childhood ALEs exhibited HPA axis dysregulation. Results showed that mothers with histories of childhood abuse had lower CORT reactivity to a psychosocial and physical stressor during the postpartum period (Brand et al., 2010). Results also showed, however, that current maternal depressive symptoms, recent stressful events, and a history of PTSD moderated the effects of childhood ALEs on CORT reactivity to the stressors (Brand et al., 2010).

Latinas in the U.S. and abroad are at substantially greater risk of experiencing ALEs due to poverty, discrimination, and lifetime histories of abuse (Garcia-Esteve et al., 2014; Kuo et al., 2004; Lucero et al., 2012) and as noted previously are at substantially greater risk to develop PND. Nonetheless, few studies have examined the association between ALEs and perinatal depression in Latinas and none has investigated the role that HPA axis dysregulation may play in the elevated risk for perinatal depression seen in Latinas. Previously, we developed a conceptual model of risk for postpartum depression in Latinas that hypothesized HPA axis dysregulation may serve as a pathophysiological mediator of risk linking ALEs to vulnerability to develop depression in the perinatal period (Lara-Cinisomo, Girdler, Grewen, & Meltzer-Brody, 2016). Consequently, the primary aim of this exploratory study was to examine univariate relationships between ALEs, PND, and HPA axis stress reactivity to a physical stressor – the hand cold pressor test (CPT) in a sample of Latinas during the perinatal period.

A secondary aim of the study was to explore whether HPA axis responses to the CPT predicted sensitivity to that test. While the CPT activates stress-responsive axes, including the HPA and sympathetic nervous system axes (Godfrey et al., 2014; Santa Ana et al., 2006; Schwabe, Haddad, & Schachinger, 2008), and is commonly used as a physical stressor in laboratory studies, it is also a potent noxious stimulus (Girdler et al., 2005; Gordon, Johnson, Nau, Mechlin, & Girdler, 2017; Light et al., 1999). Consistent with a stress-induced, endogenous pain regulatory mechanism (Choi, Chung, & Lee, 2012; Geva, Pruessner, & Defrin, 2014; Hannibal & Bishop, 2014; Paananen et al., 2015), studies in non-clinical samples generally find a positive correlation between cortisol levels and tolerance to noxious stimuli, including the CPT (Mechlin, Maixner, Light, Fisher, & Girdler, 2005; Sudhaus et al., 2015). Additionally, reduced diurnal variation of cortisol, a reflection of HPA

axis dysregulation, is correlated with increased pain sensitivity in response to the CPT (Godfrey et al., 2014).

It is well established that clinical pain and somatic symptoms are associated features of depression (Corruble & Guelfi, 2000; Simon, VonKorff, Piccinelli, Fullerton, & Ormel, 1999). While 30–77% of women experience pain following childbirth (Fitzgerald, 2013), problematic and persistent pain can increase a woman's risk for PND. Recent evidence suggests that problematic postpartum pain (e.g., vaginal, cesarean, back, etc.) and PND occur together at higher-than-expected rates (Bair, Robinson, Katon, & Kroenke, 2003). Within the perinatal period, pain sensitivity is an important factor to consider in women with respect to understanding perinatal mood disturbance because heightened pain sensitivity, particularly related to breastfeeding, has also been implicated in premature weaning (Indraccolo, Bracalente, Di Iorio, & Indraccolo, 2012), which has itself been associated with PPD (Hatton et al., 2005). The possibility exists that dysregulation in the HPA axis response to stress represents a potential shared mechanism linking depression, including perinatal depression, to heightened pain sensitivity. This is supported, in part, by studies showing that elevated depressive symptoms are associated with attenuated CORT response to psychological stress (Burke, Davis, Otte, & Mohr, 2005).

To address our study aims, we examined relationships between PND assessed longitudinally from third trimester of pregnancy to 4 and 8 weeks postpartum, and the relationship of depression to ALEs, as well as to HPA axis stress reactivity and sensitivity to the CPT assessed at 8 weeks postpartum. The primary objective of this exploratory, laboratory-based study was to examine evidence for associations between ALEs, HPA axis response to physical stress and PND in Latinas. The secondary aim was to assess whether there was evidence for HPA-axis endogenous pain regulation of sensitivity to the CPT and whether there were differences by PND status. The results of this study are intended to generate mediational hypotheses to test in a larger sample of Latinas.

Material and Methods

Sixty-five prospective participants were screened during routine prenatal visits at a local hospital and nearby community centers by trained English- and Spanish-speaking female research assistants (RA) and 34 were enrolled. To be eligible to participate, women had to self-identify as Latinas; have a singleton pregnancy; be able to read, write, and speak English or Spanish; and be willing to be followed until eight weeks postpartum. This exploratory study was conducted within the context of a larger program of research involving a birth cohort of Latinas - the Study of Exposure to stress, Postpartum mood, Adverse life events, and Hormonal function among Latinas (SEPAH Latina). Because one of the primary aims of SEPAH Latina was to examine breastfeeding practices, oxytocin mechanisms and PND (results reported elsewhere –(Lara-Cinisomo, Plott, Grewen, & Meltzer-Brody, 2016; Lara-Cinisomo, McKenney, Di Florio, & Meltzer-Brody, in press), we intentionally recruited women who intended to breastfeed 2 months. Exclusion criteria included reported maternal or infant disorder that might interfere with breastfeeding, maternal substance use, and current or past severe psychiatric disorder other than unipolar depression or anxiety (e.g., bipolar disorder).

The study was approved by the University of North Carolina, Chapel Hill Institutional Review Board. Women gave written consent prior to enrollment and were compensated after each interview. For this study, women were assessed three times: 1) in the third trimester of pregnancy during the enrollment session where demographic information was collected; 2) at four weeks postpartum via phone interview; and 3) at eight weeks postpartum during a laboratory visit.

Measures

Perinatal Depression—Depression status was assessed at each time point using the English- and Spanish validated Edinburgh Postpartum Depression Scale (EPDS; (J. L. Cox, Holden, & Sagovsky, 1987; L. s. Garcia-Esteve, Ascaso, Ojuel, & Navarro, 2003). The EPDS is a 10-item instrument widely used to assess depression post-delivery and has also been shown to be valid during the prenatal period (Kozinszky & Dudas, 2015). Responses are based on a 4-point scale (0, 1, 2, and 3) and responses are summed to produce a total score, with a maximum score of 30. Depression was operationally defined using the cutoff for minor and major depression (EPDS ≥ 10 ; (J. L. Cox, Chapman, Murray, & Jones, 1996; Gaynes et al., 2005), which has been shown to be a reliable cut point for Latinas (Howell et al., 2012). The Structured Clinical Interview for the DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 1997) was used at enrollment to collect depression histories.

Adverse life events—Adverse life events were ascertained at enrollment using the SCID, which captures childhood and adult-related ALEs as well as infant-related adversity such as loss of an infant and premature birth, and intimate partner violence. Additionally, a trained RA or the Principal Investigator administered a structured ALEs interview at 8 weeks postpartum. This interview captured childhood abuse, including sexual and physical abuse, as well as other ALEs before 18 years of age (J. Leserman et al., 1997; Jane Leserman et al., 2007). This instrument has been shown to reliably assess ALEs and to be associated with PND (Pedersen et al., 2016).

Physical Stressor, pain assessment and collection of biomarkers—At 8 weeks postpartum, women were invited to the hospital where they participated in a controlled laboratory experiment that began at 9:00 a.m. for all participants. As part of the larger aims of the SEPAH Latina study, women were instructed to allow for at least a 90-minute window between the at-home morning feeding and the scheduled laboratory visit to ensure the child would be hungry during an observed feeding session. The laboratory protocol was modeled after a recent prospective study of PPD, lactation and neuroendocrine function in non-Latina women (Stuebe, Grewen, & Meltzer-Brody, 2013) and extended this work to include HPA axis modulation of pain sensitivity. Participants were seated in a comfortable chair where a trained nurse placed an intravenous (IV) catheter in an antecubital vein; the IV remained in place for the duration of the laboratory experiments and the nurse remained in the room, behind a curtain during the entire laboratory protocol. Participants remained in the chair and read home improvement magazines for the 10-minute habituation period. The first condition involved an infant feeding session where women were asked to either breast- or bottle-feed their infant for at least 10 minutes (results reported elsewhere; Lara-Cinisomo et al., in press).

Plasma ACTH and serum CORT were collected via IV by a trained nurse 10 minutes following the infant feeding session and these levels constituted the pre-stressor rest levels for the current report. After a ten-minute rest, women participated in the CPT to assess pain sensitivity and HPA axis function. The CPT is one of the most frequently used procedures to measure pain sensitivity in a laboratory setting (Koenig et al., 2014; McGinley & Friedman, 2015). Participants submerge their hand in ice water, eliciting a strong sympathetic nervous system stress response and activation of the HPA axis. To maximally activate the HPA axis, participants were video-recorded using a video camera propped on a tripod in front of them (Schwabe et al., 2008). Participants submerged their hand in a container filled with ice and water set at 3.5°C (38.5°F) and maintained at that temperature using a water-circulating device. To prevent tissue damage, a maximum time limit of 5 minutes was imposed. Participants were instructed to report when the sensations in their hand first became painful, allowing us to determine pain threshold measured in seconds and when they were no longer willing or able to tolerate the pain to capture pain tolerance measured in seconds. The RA showed a visual analog scale (VAS) that ranged from 0 “No pain intensity” to 100 “Strongest imaginable pain intensity of any kind” to the women and asked them to verbally rate pain intensity before removing their hands from the ice bath. Participants also verbally reported levels of pain unpleasantness using a VAS ranging from 0 “No unpleasantness” to 100 “Most unpleasant pain of any kind imaginable.” The RA recorded participant ratings using pencil/pen on the laboratory protocol sheet. Plasma ACTH pg/ml and serum CORT ug/dl were collected again 20 minutes after the onset of the CPT stressor. This time point was selected based on the consistent evidence that CORT peaks within 10–30 minutes following stress onset (Arvat et al., 2000; S. M. Smith & Vale, 2006).

Statistical Analysis

Descriptive statistics were computed to characterize the sample. Logistic regressions were conducted to test the probability of prenatal depression predicting current postpartum depression. Fisher’s exact tests were conducted to assess associations between categorical variables, and one-way analysis of variance (ANOVA) were conducted to determine associations between categorical predictors (e.g., any childhood ALE coded as yes/no) and continuous outcomes (e.g., ACTH, depression scores). Pearson correlations were conducted to assess the association between pain measures and hormone levels. We conducted correlations and ANOVAs to assess associations between ALEs and neuroendocrine function. We used ANOVA to explore reactivity in ACTH and CORT to the CPT in the entire sample, by depression status, and by type of ALE. HPA stress reactivity was defined as post-CPT ACTH or CORT concentration minus baseline, pre-CPT concentrations. Where significant differences in reactivity emerged, paired t-tests were conducted to examine the source of the difference. Given the skewedness of plasma ACTH levels in the sample, the log of ACTH is used in our analysis. Although multiple tests were conducted in this exploratory study, we did not control for Type 1 error rate because of the pilot nature of the research. P-values less 0.05 were interpreted as significant. Due to the limited sample size, these models did not control for any other participant characteristics. All comparisons among means are thus performed without any a priori expectation, therefore no adjustment for multiple significant testing was employed (Bender & Lange, 2001). All of the analyses were conducted using SPSS 23 (IBM_Corp., 2015).

Neuroendocrine Assays

ACTH Radioimmunoassay—Plasma ACTH levels were measured using a commercially available double antibody radioimmunoassay kit and protocol available from MPBiomedicals, Orangeburg, NY. Samples do not require extraction. Samples were incubated with anti-ACTH and hACTH-125I at 4°C for 24 hours. Following a brief incubation with a second antibody precipitating reagent, the ¹²⁵I-ACTH bound to the antibody complex were separated from free by a 40-minute centrifugation at 1700xg. Radioactivity in the pellet was measured using a Perkin Elmer 1470 Wizard gammacounter, which calculates the pg/ml content of ACTH in each sample from the standard curve. The ACTH assay has a sensitivity of 5.7 pg/ml with a standard range of 10 to 1000pg/ml. The intra- and inter- assay variation is 4.1% and 3.9%, respectively.

Cortisol Radioimmunoassay—Serum cortisol levels were assessed using a commercially available coated tube radioimmunoassay kit and protocol from MP Biomedicals, Solon, OH. The cortisol assay has a sensitivity of .07 ug/dl with a standard range of 1 to 60 ug/dl. The intra- and inter-assay variation is 4.7 and 7.6%, respectively.

Results

As Figure 1 shows, 34 women were enrolled, two women were lost to follow-up at 4 weeks and two were lost prior to the 8-week postpartum laboratory visit. Of the four lost to follow-up, one woman had PND at enrollment. Thirty women attended the laboratory visit at 8 weeks postpartum. Two nondepressed women had difficult-to-access veins, which prohibited us from drawing blood. Of the 28 whose blood was drawn, one sample was excluded from the hormone analyses because there were extraction issues during assaying; this woman had PND. Because the focus of this report is on the univariate relationships involving PND, ALEs, hormones, and pain sensitivity, all analyses were restricted to these 27 women with complete data.

Of the 27 women with complete data, 82% percent were Spanish speaking and 85% were immigrant. More than three quarters were married or cohabitating (85%) and most were multiparous (63%). At enrollment, seven of the 27 women (26%) met the cutoff for minor or major depression (EPDS ≥ 10); five women met the criteria at 4 weeks postpartum (18%) and five women met the criteria at 8 weeks postpartum (18%). According to the SCID, more than half (56%) had a history of major depression and 15% of those had a history of postpartum onset. Results from the logistic regressions indicate that prenatal depression determined at enrollment using the EPDS was significantly predictive of PND at 4 weeks and 8 weeks ($\beta = 3.23$, $p = 0.012$, respectively). Depression at 4 weeks was also predictive of PND at 8 weeks ($\beta = 4.43$, $p = 0.003$). There was a marginally significant association between depression history based on the SCID and prenatal depression ($\beta = -1.87$, $p = 0.058$), but none with depression at 4 weeks ($\beta = 0.000$, $p = 1.000$) or 8 weeks ($\beta = -1.03$, $p = 0.318$).

Perinatal Depression and Adverse Life Events (ALEs)

Fourteen of the 27 women (52%) reported at least one childhood ALE. Physical abuse was the most commonly reported type of childhood ALE ($n = 7$), followed by sexual abuse ($n = 6$), and childhood verbal abuse ($n = 4$). Four women reported death of a parent and two experienced parent abandonment prior to the age of 18. With regard to adulthood ALEs, seven women reported a history of intimate partner violence (IPV) and four women reported infant-related adversity experienced in adulthood (e.g., infant demise). With regard to lifetime ALEs, five women reported more than one form of childhood and adulthood abuse.

As summarized in Table 1, women who reported at least one form of childhood ALE had, on average, higher mean EPDS depression scores over the three assessment periods (pre-, 4 weeks, and 8 weeks postpartum). However, the relationship between a history of childhood ALEs and greater depressive symptomatology was greatest for prenatal depression scores ($F(1, 25) = 5.69, p = 0.025$). A marginally significant association for depression scores at 8 weeks postpartum was found ($F(1, 25) = 3.35, p = 0.08$), while a history of childhood abuse did not predict depression symptom scores at 4 weeks postpartum ($F(1, 25) = 0.001, p = 0.974$). A similar pattern was observed among women who reported at least one infant-related ALEs and PND, though no significant associations were observed.

HPA axis response to the CPT

There was a significant positive correlation between ACTH reactivity (post ACTH – pre ACTH) ($r = 0.98, p = 0.000$, not shown) and CORT reactivity to the CPT (post CORT – pre CORT) ($r = 0.71, p = 0.000$, not shown). As Table 2 shows, the mean pre-CPT ACTH levels of 4.49 ($SD = 0.51$) and the mean post-CPT levels of 4.47 ($SD = 0.57$), indicate no ACTH response to the CPT in the sample as a whole ($t(26) = 1.22, p = 0.233$). In the sample as a whole, the mean pre-CPT CORT levels was 8.13 ($SD = 5.13$) and the post-CPT CORT levels was 8.53 ($SD = 6.47$), a difference that was not statistically significant in the sample as a whole ($t(26) = -0.46, p = 0.652$).

Mothers' self-reported ALEs and HPA axis stress reactivity

Table 3 shows that with the exception of women with a history of an infant-related ALE, ACTH levels decline from pre to post-CPT. Additional analysis revealed that any infant-related ALE was associated with greater ACTH reactivity ($F(1, 25) = 5.29, p = 0.030$). Subsequent analyses indicated that this difference resulted because women without infant-related ALEs exhibited a significant decrease in ACTH reactivity from pre- to post-CPT ($t(22) = -2.39, p = 0.026$) while women with infant-related ALEs showed a nonsignificant increase ($t(3) = 0.99, p = 0.393$). There was also a pattern of reduced post-CPT ACTH levels in all women who experienced any form of ALE, though only a history of any childhood ALE proved significant. Specifically, there was also a significant association between any childhood ALE and CORT reactivity to the CPT since those with any childhood ALE exhibited blunted CORT reactivity ($F(1, 25) = 4.41, p = 0.045$). Subsequent t-tests indicated that women with any childhood ALE exhibited a marginally significant decrease in CORT response to the CPT ($t(13) = -1.96, p = 0.072$) while there was no significant change in women with no history of childhood ALEs ($t(12) = 1.41, p = 0.185$) (see Figure 2).

Perinatal Depression Status and HPA axis stress reactivity

When comparing women with versus without PND at 4 weeks postpartum, those with PND had greater ACTH stress reactivity to the CPT than those without PND ($F(1, 25) = 5.55$, $p = 0.027$) at 8 weeks postpartum when stress reactivity was assessed. As Figure 3 illustrates, this is because women without PND exhibited a significant decrease in ACTH in response to the CPT ($t(21) = -2.45$, $p = 0.023$) while those with PND showed no response ($t(4) = p = 1.11$, $p = 0.329$). Though only marginally significant differences were found in ACTH reactivity by prenatal depression ($F(1, 25) = 3.55$, $p = 0.071$) and none were observed by PND at 8 weeks ($F(1, 25) = 1.54$, $p = 0.226$), a similar pattern was observed in those *without* PND in pregnancy and at 8 weeks postpartum who tended to exhibit blunted ACTH reactivity ($t(19) = -2.29$, $p = 0.034$ and $t(21) = -1.80$, $p = 0.087$, respectively), while those with PND showed no ACTH reactivity to the CPT ($t(6) = 0.77$, $p = 0.472$ and $t(4) = 0.436$, $p = 0.685$, respectively).

Regarding CORT, Table 2 shows a general pattern of blunted reactivity to the CPT in those with PND at any time point relative to those without PND. Women with PND showed a decrease in CORT from pre- to post CPT ($t(20) = 1.00$, $t(21) = 0.67$, $t(21) = 0.76$, $ps > 0.330$) while those without PND showed an increase from pre- to post-CPT ($t(6) = -1.97$, $t(4) = -0.83$, $t(4) = -1.07$, $ps > 0.097$), though these differences were not statistically significant.

Relationship of PND to pain sensitivity to the CPT

Pain tolerance was positively and significantly correlated with pain threshold in the full sample ($r = 0.428$, $p < 0.026$, not shown). As Table 4 shows, on average, pain threshold was reported at 17.22 (SD = 8.59) seconds and pain tolerance was reported at 39.44 (SD = 53.75) seconds after the onset of the CPT stressor. Women who had suffered depression at any study time point showed a pattern of lower mean pain threshold ($F(1, 25) = 2.41$, 0.97, 0.21, $ps > 0.133$) and tolerance times compared to non-depressed women, though these differences were not statistically significant ($F(1, 25) = 0.96$, 0.46, 0.34, $ps > 0.336$).

Also shown in Table 4, on average, at the point of pain tolerance, women reported a mean pain intensity rating of 63.52 (SD = 20.98) and pain unpleasantness rating of 69.74 (SD = 24.67) based on a 0 to 100 visual analogue scales. While not statistically significant, results shown in Table 4 suggest a pattern of higher pain intensity ratings in response to the CPT ($F(1, 25) = 0.38$, 0.41, 1.27, $ps > 0.271$), but lower mean pain unpleasantness ratings $F(1, 25) = 3.73$, 2.30, 0.45, $ps > 0.065$) among depressed versus non-depressed women.

Pain sensitivity and relationship to HPA axis measures

Cortisol reactivity to the CPT stressor showed the most consistent relationships with pain sensitivity. In keeping with endogenous pain regulation by HPA axis reactivity, there was a positive and significant correlation between pain tolerance and CORT reactivity to the CPT ($r = 0.453$, $p = 0.018$) (see Table 5). Although the correlations between CORT reactivity and pain threshold, intensity, and unpleasantness are in directions consistent with analgesic effects, they did not reach statistical significance ($r = 0.21$, -0.15 , -0.16 , respectively; $p > 0.294$).

Discussion

This is the first study to examine associations between ALEs, HPA axis stress reactivity, and PND in a sample of Latinas. As expected, we found that women with a history of any childhood ALE had generally higher depressive symptom scores at each of the pre- and postnatal time points but particularly so during the prenatal period. These findings support previous studies highlighting the vulnerability to PND in women with early life abuse histories (Alvarez-Segura et al., 2014; Buist & Janson, 2001; Faisal-Cury et al., 2013; Meltzer-Brody et al., 2013; Plaza et al., 2012; Rodríguez et al., 2010).

A history of childhood ALEs has also been shown to predict HPA axis dysregulation in adulthood (Heim et al., 2008), and while our results support these previous findings, they are novel in the focus on Latina women in the perinatal period. We observed that women with a history of ALEs, including infant-related adversity and childhood abuse, exhibited greater ACTH reactivity and blunted CORT reactivity, respectively, to the CPT in comparison to women without such a history. These findings are consistent with other studies in women with childhood abuse (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001), but this has not been tested in women with infant-related adversity. While there is evidence of the deleterious effects infant-related ALEs can have on women's mental health (Reynolds, 1997), less is known about the physiological consequences of such events on stress reactivity. This is among the first studies to explore these associations. Future studies should examine links between infant-related ALEs and neuroendocrine function in mothers.

The significant effects that we obtained demonstrating greater ACTH but blunted CORT stress reactivity in those with a history of ALEs mirror the pattern of results when HPA axis stress reactivity was examined as a function of PND status. Those with PND at four weeks postpartum had significantly greater ACTH reactivity to the CPT and, although not significant, there was a general pattern for blunted CORT stress reactivity in women with depression at any time point in the study. This HPA axis profile is worth comment. First, the greater ACTH reactivity, which represents the central drive by the pituitary on the adrenal cortex, in combination with blunted CORT reactivity, suggests possible impairment in negative feedback mechanisms regulating homeostasis of the HPA axis (Kumar et al., 2006). This HPA axis pattern was common to both those with perinatal depression and those with a history of ALEs suggesting a potential shared mechanism of risk that links a history of ALEs to PND. Second, it is noteworthy that in the analyses as a function of ALEs and in the analyses as a function of PND, where significant differences in ACTH reactivity emerged, they were driven by the non-affected groups who showed a significant decrease in ACTH in response to the CPT stressor. These findings support previous findings with non-Latina mothers (Jolley et al., 2007), where women without PND exhibited a decreased ACTH response to stress. It is interesting to speculate that the perinatal period provides a unique context for HPA axis reactivity given the adaptive state of high cortisol in pregnancy and the naturally-occurring reduction of that hormone and that reduced central drive on the adrenal cortex in response to stress may be adaptive during pregnancy and in the immediate postpartum period. This is an emerging area of inquiry that requires further investigation, particularly within the context of PND.

This study further documented in a sample of postpartum Latina women the expected relationship between greater CORT reactivity to the CPT stressor and increased pain tolerance, when analyzed in the sample as a whole, which is congruent with the expected HPA axis endogenous pain regulatory effect (Godfrey et al., 2014; Mechlin et al., 2005). To the extent that greater cortisol reactivity to the CPT would be expected to be associated with decreased sensitivity to painful stimuli, the pattern of blunted cortisol reactivity to the CPT seen in women with depression at all time points relative to their non-affected counterparts may have contributed to their general pattern of enhanced sensitivity to cold pressor pain (reflected in their nonsignificant pattern of lower pain threshold and tolerance times and higher pain intensity ratings). While speculative, the diminishment of endogenous pain regulation by blunted cortisol reactivity to stress may represent an additional form of HPA axis dysregulation in Latina women with perinatal depression that would have relevance not only to affect but to the experience of somatic symptomatology in the postpartum period. This interpretation is consistent with the evidence that dysregulation of the HPA axis is associated with altered sensory response to pain (Kuehl, Michaux, Richter, Schächinger, & Anton, 2010).

Further exploration of pain processing in PND is recommended given the observed pattern of lower pain threshold and tolerance and reported higher pain intensity to the CPT in women with PND compared to non-depressed women. The trends are congruent with previous studies showing that depressed populations report higher pain intensity (Mok & Lee, 2008). We also found that women with PND reported marginally significant lower pain unpleasantness ratings than nondepressed women, which was not expected. The dissociations between pain intensity and pain unpleasantness in those with depression is intriguing. One possible explanation for lower pain unpleasantness ratings in those with depression might result from the fact that the unpleasantness dimension of pain perception reflects the affective or emotional properties of pain, and depressed women might experience less emotional responsiveness than nondepressed women (Sloan, Strauss, Quirk, & Sajatovic, 1997), whereas pain intensity reflects the sensory, discriminatory properties of pain (W. B. Smith, Gracely, & Safer, 1998). An alternative explanation could be found in neurological activation of emotional processing regions in the brain. For example, depressed women might exhibit less activation in regions, such as the ventromedial prefrontal cortex (Berna et al., 2010), the amygdala, and the anterior cingulate cortex (Berna et al., 2010), which have been implicated in pain and emotion processing, and depression. Recent neuroimaging studies revealed dysregulation in related brain regions in mothers with PPD (Moses-Kolko et al., 2010). Further examination using neuroimaging strategies might help elucidate the dissociation found between pain intensity and pain unpleasantness in our depressed Latina mothers.

Conclusions

This study is the first to explore relationships among ALEs, PND and HPA axis responses to a cold pressor test in a birth cohort of Latinas. Our findings showed significant univariate relationships, even in this small sample, between: 1) ALEs and PND; 2) ALEs and HPA axis stress reactivity; and 3) PND and HPA stress reactivity, providing supportive evidence for testing a mediational model of PND development in Latinas (Lara-Cinisomo et al., 2016).

Our secondary analyses involving pain sensitivity to the CPT in this sample, while not yielding statistically significant findings, are worth examining in a larger sample given the consistent pattern of results for heightened pain sensitivity during the postpartum period in Latinas with prenatal and postpartum depression. However, this study is not without limitations. First, our sample size was very small. As Table 2 shows, the depressed groups had large standard errors compared to the nondepressed groups. This speaks to our small sample size and high Type II error rates, which prevented us from detecting significant effects. Still, while its small sample size limits definitive conclusions, the study's findings are meant to serve a heuristic value for future research in this vulnerable population. A second notable limitation was the limited number of neuroendocrine sampling points following the onset of the CPT, which hampered our ability to examine the full neuroendocrine response to the stressor. Third, our study lacked information regarding medication use, which might have affected neuroendocrine results.

Implications for Practice

This first-of-its-kind study shows interesting findings, including those suggesting that information taken during a clinical history, such as ALEs and depressive symptom levels, are predictive of HPA axis reactivity in Latina women during the postpartum period. Our finding that cortisol reactivity to stress served as an endogenous modulator of pain sensitivity in this sample suggests that the blunted cortisol reactivity to stress observed in those with a history of ALEs or with PND may have implications for modulation of clinical pain sensitivity in Latina women during the perinatal period. While this needs to be empirically tested, if confirmed, it could influence breastfeeding practices in those women with PND. As such, our findings demonstrate the potential for future research with this highly vulnerable population, which should include larger numbers of Latinas with or without a history of adverse events to better estimate the association between pain sensitivity, HPA axis function and PND to increase the duration of breastfeeding and improve maternal outcomes. A larger sample of Latinas will also provide investigators with the necessary statistical power to test the hypotheses generated here. The proposed lines of research will allow investigators to explore multi-variable models that integrate variables, such as the timing of ALEs, stress reactivity, breastfeeding practices, and PND to test various causal pathways. Future studies might explore the interaction between these factors, as well as the modifying effect of predictors (e.g., ALEs) on PND to better inform treatment approaches and clinical care.

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Figure 1.
Participant flow chart

Figure 2.
Mean serum CORT Concentration Levels at Baseline and in Response to the CPT by History of Any Childhood ALE Measured at 8 weeks Postpartum (n= 27)

Figure 3. Mean Log transformed plasma ACTH Concentration Levels at Baseline and in Response to the CPT by 4 week PND Measured at 8 weeks Postpartum (n= 27)

Table 1

Adverse Life Events (ALE) by Mean Perinatal Depression Score based on the EPDS (Standard Deviations reported in parenthesis) (n = 27).

	Prenatal depression score	4 week postpartum depression score	8 week postpartum depression score
Any Childhood ALE			
No (n = 13)	3.92 (3.28)	5.08 (4.59)	2.85 (3.85)
Yes (n = 14)	7.86 (5.04) *	5.14 (5.84)	6.00 (4.98)
Any Adulthood ALE			
No (n = 21)	6.57 (5.03)	5.90 (5.38)	5.00 (5.04)
Yes (n = 6)	3.83 (2.14)	2.33 (3.39)	2.67 (2.58)
Any infant-related ALE			
No (n = 23)	5.57 (4.18)	4.57 (4.60)	4.30 (4.87)
Yes (n = 4)	8.25 (7.18)	8.25 (7.85)	5.50 (3.70)
Total (N = 27)	5.96 (4.65)	5.11 (5.18)	4.48 (4.67)

Notes:

*
p < 0.05

Table 2
Mean (+SEM) HPA axis measures at baseline and in response to CPT by depression status (n=27)

	Prenatal Depressed (n = 7)	Prenatal Nondepressed (n = 20)	4 weeks Postpartum Depressed (n = 5)	4 weeks Postpartum Nondepressed (n = 22)	8 weeks Postpartum Depressed (n = 5)	8 weeks Postpartum Nondepressed (n = 22)	All women at 8 weeks Postpartum (n = 27)
LogACTH (pg/ml)							
Pre-CPT	4.68 (0.36)	4.43 (0.06)	4.87 (0.48)	4.41 (0.05)	4.96 (0.45)	4.39 (0.06)	4.49 (0.10)
Post-CPT	4.72 (0.39)	4.37 (0.06)	4.94 (0.53)	4.36 (0.05)	4.99 (0.51)	4.35 (0.05)	4.47 (0.11)
Reactivity to CPT	0.042 (0.05)	-0.052 (0.02)	0.08 (0.07) ^a	-0.05 (0.02)	0.03 (0.07)	-0.04 (0.02)	-0.03 (0.02)
Cortisol (ug/dL)							
Pre-CPT	9.49 (2.87)	7.66 (0.92)	10.04 (4.12)	7.70 (0.84)	10.42 (4.04)	7.61 (0.84)	8.13 (0.99)
Post-CPT	7.85 (2.30)	8.77 (1.50)	9.12 (3.12)	8.40 (1.39)	9.14 (3.11)	8.40 (1.39)	8.53 (1.24)
Reactivity to CPT	-1.63 (0.83)	1.11 (1.11)	-0.93 (1.11)	0.70 (1.04)	-1.28 (1.20)	0.78 (1.03)	0.40 (0.88)

Notes:

^aDepressed at 4 weeks postpartum > Not Depressed at 4 weeks postpartum, p < .05.

Table 3

Mean (+SEM) HPA axis measures at baseline and in response to CPT by ALE (n=27)

	Any childhood ALE		Any adulthood ALE		Any infant-related ALE	
	No (n = 13)	Yes (n = 14)	No (21)	Yes (6)	No (23)	Yes (4)
LogACTH (pg/ml)						
Pre-CPT	4.39 (0.09)	4.59 (0.17)	4.51 (0.13)	4.43 (0.10)	4.44 (0.07)	4.82 (0.59)
Post-CPT	4.36 (0.08)	4.56 (0.20)	4.49 (0.14)	4.36 (0.08)	4.39 (0.07)	4.92 (0.66)
Reactivity to CPT	-0.03 (0.04)	-0.03 (0.03)	-0.02 (0.03)	-0.07 (0.05)	-0.05 (0.02)	0.09 (0.00)*
Cortisol (ug/dl)						
Pre-CPT	8.24 (1.00)	8.03 (1.71)	8.49 (1.14)	6.88 (2.09)	8.63 (1.12)	5.28 (1.15)
Post-CPT	10.44 (2.15)	6.76 (1.23)	9.04 (1.52)	6.77 (1.70)	9.14 (1.42)	5.06 (0.86)
Reactivity to CPT	2.02 (1.56)	-1.27 (0.65)*	0.54 (1.02)	-0.11 (1.81)	0.51 (1.03)	-0.22 (0.61)

Notes:

* $p < .05$

Table 4

Mean (SD) Pain outcomes measured at postpartum week 8 as a function of depression status over the course of the study (N = 27)

	Prenatal Depressed (n = 7)	Prenatal Nondepressed (n = 20)	4 weeks Postpartum Depressed (n = 5)	4 weeks Postpartum Nondepressed (n = 22)	8 weeks Postpartum Depressed (n = 5)	8 weeks Postpartum Nondepressed (n = 22)	All women at 8 weeks (n = 27)
EPDS	12.43 (3.21)	3.70 (2.36)	14.00 (1.58)	3.09 (3.10)	12.00 (1.87)	2.77 (3.13)	4.48 (4.67)
Pain Threshold	13.00 (9.29)	18.70 (8.05)	13.80 (10.28)	18.00 (8.23)	15.60 (9.07)	17.59 (8.65)	17.22 (8.59)
Pain Tolerance	22.29 (12.87)	45.45 (61.28)	24.60 (14.28)	42.82 (58.94)	26.60 (13.44)	42.36 (59.11)	39.44 (53.75)
Pain Intensity	59.29 (25.24)	65.00 (19.80)	69.00 (23.02)	62.27 (20.86)	73.00 (24.90)	61.36 (21.01)	63.52 (20.98)
Pain Unpleasantness	55.00 (24.32) ^a	74.90 (23.19)	55.00 (23.98)	73.09 (24.09)	63.00 (24.29)	71.27 (25.03)	69.74 (24.67)

Notes:

^a prenatal depressed < prenatal nondepressed p = 0.065

Table 5

Pearson Correlations with Pain Measures and Stress Hormones measured at 8 weeks postpartum (N = 27)

	LogACTH Baseline	LogACTH +20 Response	LogACTH Reactivity	CORT Baseline	CORT +20 Response	CORT Reactivity
Pain Threshold (seconds)	0.040	-0.018	-0.258	-0.175	0.009	0.210
Pain Tolerance (seconds)	0.052	0.059	0.055	-0.016	0.306	0.453 *
Pain Intensity Rating (0-100)	0.128	0.099	-0.085	0.117	-0.016	-0.154
Pain Unpleasantness Rating (0-100)	-0.010	-0.055	-0.217	-0.062	-0.159	-0.156

Notes:

* $p < .05$