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ORIGINAL ARTICLE

Early life adversity and depressive symptoms predict cortisol in pregnancy

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Abstract

Evidence suggests that exposure to early life adversity (ELA) programs the hypothalamic-pituitary-adrenal (HPA) axis to influence responses to later adversity and predisposes women to depression. However, few studies have examined whether ELA moderates the HPA cortisol response to adulthood adversity and depressive symptoms in pregnant women. The aims of this study were to determine (a) whether ELA, adulthood adversity, and depressive symptoms differentially predict patterns of cortisol and (b) whether ELA moderates the relationship of adulthood adversity or depressive symptoms to cortisol. This was a descriptive, cross-sectional study of pregnant women ($N = 58$, mean = 26.5 weeks gestation). Participants completed the Stress and Adversity Inventory and Edinburgh Depression Scale and collected salivary cortisol five times per day for 3 days to assess cortisol awakening response (CAR), diurnal cortisol slope, and cortisol area under the curve (AUC). ELA predicted a larger CAR, while depressive symptoms predicted a blunted CAR and higher cortisol AUC. Adulthood adversity predicted a blunted CAR and steeper diurnal slope, but only in women with high ELA. ELA also moderated the effect of depressive symptoms on diurnal slope. Early adversity and depressive symptoms appear to have significant effects on the HPA axis during pregnancy, with early adversity also moderating effects of depressive symptoms and adulthood adversity on cortisol regulation. Early adversity may be an important factor in identifying unique HPA phenotypes and risk for HPA axis dysregulation in pregnancy.

Keywords HPA · Childhood trauma · Stress · Hardship · Prenatal

Women's exposure to life course adversity is associated with long-term psychosocial, biobehavioral, and neuroendocrine adaptations, all of which converge to influence health trajectories over the life course (Felitti et al. 1998; Heim et al. 2008).

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While the role of stress *during* pregnancy has received much attention, relatively less is known about the effects of pre-pregnancy life course adversity, especially as it relates to neuroendocrine regulation of the stress response. In pregnant women, exposure to early life adversity (ELA) is associated with poor reproductive outcomes, including preterm delivery, small for gestational age neonates, and longer hospital stays (Smith et al. 2016; Miller et al. 2017). However, ELA strongly predisposes women to depression (Nelson et al. 2017), which must be considered concurrently as a related factor. Adverse pregnancy outcomes may be influenced by the effects of exposure to adverse experiences and depressive symptoms on the hypothalamic-pituitary-adrenal (HPA) axis, especially via variations in maternal cortisol regulation (Buss et al. 2009; Gillespie et al. 2017). The purpose of the study described here was to examine the differential effects of early adversity, adult adversity, and prenatal depressive symptoms on cortisol parameters during pregnancy.

Relative to adulthood, neurodevelopment during childhood and adolescence is more plastic and susceptible to

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programming influences from stressful environmental and social contexts (Gee and Casey 2015). Pregnant women with a history of ELA show variations in cortisol regulation (Bublitz and Stroud 2012) which mediate effects on offspring stress reactivity (Thomas et al. 2018a). Furthermore, higher stress and adversity during adulthood is associated with alterations in the stress response during pregnancy (Rice and Records 2006, 2008; Thayer and Kuzawa 2014). However, these findings have not been consistent across all studies (Bleker et al. 2017).

Depressive symptoms are also associated with variations in cortisol, including a blunted cortisol awakening response (CAR), flatter diurnal slopes across the day, and elevated basal cortisol later in the day (Chida and Steptoe 2009; Hsiao et al. 2010). These changes are evident even in individuals with mild or sub-clinical levels of depressive symptoms (Dedovic and Ngiam 2015). In contrast, major depressive episodes are *preceded* by a larger CAR, which may link larger CAR observed with ELA and greater risk for subsequent depression (Vrshek-Schallhorn et al. 2013). Cortisol alterations in depressed individuals are linked with unfavorable depressive symptom trajectories over time (Vreeburg et al. 2013) and poor depression treatment response (Fischer et al. 2017). In pregnancy, depressive symptoms have likewise been associated with a blunted CAR (Seth et al. 2016) and elevated basal cortisol in some, but not all studies (Shea et al. 2007; Orta et al. 2018).

In addition to its direct effects on cortisol, some research suggests that ELA may moderate the relationships of later adulthood adversity or depressive symptoms with cortisol (Swales et al. 2018; Thomas et al. 2018b). Depressive symptoms and ELA together have been implicated in specific and persistent alterations in cortisol patterns in non-pregnant women (Heim et al. 2008; Seth et al. 2016), with differences in the CAR observed for depressed individuals based on history of childhood neglect (Peng et al. 2014). In pregnancy, emerging evidence suggests that ELA sensitizes the HPA response to acute stressors during pregnancy and disrupts the normal attenuation of the CAR in late pregnancy (Bublitz and Stroud 2012; Bublitz et al. 2016). Differences in the autonomic stress response of pregnant women based on abuse history have also been reported (Rice and Records 2006).

In sum, research to date suggests that early adversity, adulthood adversity, and depressive symptoms may all influence a woman's cortisol profile. But it is not clear which of these variables may have the most salient effect. In addition, a few studies indicate that early adversity may play a moderating role in whether later adversity or depressive symptoms influence cortisol response in pregnancy (Swales et al. 2018; Thomas et al. 2018b). Thus, our goal was to examine both the direct and interactive effects of the timing of adversity (i.e., occurring in early life vs. adulthood) and depressive symptoms on HPA function in pregnant women.

Our specific aims were to determine (1) whether ELA, adulthood adversity, and depressive symptoms differentially predict patterns of cortisol and (2) whether ELA moderates the relationship of adulthood adversity or depressive symptoms to cortisol in pregnancy. The findings of this study will help to identify the most important predictors of cortisol during pregnancy, and whether the persistent effects of ELA may influence cortisol response to later adversity and depressive symptoms.

Methods

Sample

In this descriptive cross-sectional study, pregnant women ($N = 58$) were recruited between January 2016 and July 2016 from an urban hospital-based obstetric clinic. Eligible participants were women aged 19 to 45 with a single intrauterine pregnancy between 20 and 28 weeks gestation ($M =$ 26.5 weeks) and able to read and speak English. Women were excluded if they had a medically high-risk pregnancy, pregnancy complications, other medical problems, or did shift work. Participant sociodemographic characteristics and descriptive statistics for study measures are summarized in Table 1.

Saliva sampling and cortisol measurement

Participants were asked to collect a total of 15 saliva samples over 3 days. Collection times included immediately upon awakening (T1), 30 min after awakening (T2), before lunch (T3), before dinner (T4), and before bedtime (T5). Participants completed a saliva collection log for each of the 3 days. In the log, participants noted the precise time of each sample and duration of prior night sleep, as well as ratings of daily stress ("Compared with a usual day, today was…" "not very stressful," "fairly stressful," or "stressful") and overall well-being ("How healthy do you feel today? "excellent," "good," "fair," or "poor"). Returned saliva samples were stored at −20 °C until processing. Samples were processed in duplicate at the University of Nebraska at Omaha (UNO) Endocrine Bioservices Laboratory by enzyme immunoassay based on methods previously described (Smith and French 1997). Duplicate cortisol values that varied by more than 20% were re-assayed. A quality control sample of pooled saliva was assayed on each plate, and the intra- and inter-assay coefficients of variation were 6.7% and 20.3% respectively. Thirty-six participants (62%) provided sufficient saliva for all 15 samples across 3 days, while all other participants provided enough saliva to calculate each cortisol parameter for at least

Table 1 Participant characteristics and descriptive statistics ($N = 58$)

	Count	Percent	Mean	± SD
Maternal age (years)			27.9	± 5.3
Maternal race				
Caucasian or White	35	60		
Black or African American	13	22		
Asian	4	7		
Other	6	10		
Hispanic ethnicity	5	9		
Completed college (associates degree or higher)	30	52		
Completed high school	50	86		
Unemployed, seeking work	10	17		
Married	29	50		
Household income < $40,000	28	48		
Primiparous	29	50		
History of preterm birth	3	5		
Pre-pregnancy BMI = overweight	27	47		
Excess pregnancy weight gain	30	52		
Smoked cigarettes	13	22		
Delivery < 39 weeks gestation	13	22		
Edinburgh Depression Scale (above cutoff)	16	28		
Score < 10 ($n = 42$)			4.6	± 2.8
Score ≥ 10 ($n = 16$)			13.2	± 3.3
Health Practices in Pregnancy Questionnaire II			139.6	± 12.1
Gestational age at cortisol collection (weeks)			26.5	± 2.4
Length of gestation (weeks)			39.5	± 1.4
Birth weight (g)			3431.9	± 463.6
Cortisol parameters				
T1			11	± 4.4
T2			12.8	± 4.8
T3			7.2	± 2.8
T4			4.5	± 1.9
T5			3.6	± 1.7
CAR			1.9	± 4.9
Diurnal slope			−0.5/h	± 0.3
AUCg			5871.7	± 1906.4
	Median	Range	Mean	± SD
Total life adversity				
Count	16	0–57	20.5	± 15.6
Severity	32	0–183	48.5	± 40.8
Early life adversity (ELA)				
Count	3	0–24	4.6	± 5.4
Severity	8	0–61	13.2	± 15.3
Adulthood adversity				
Count	13	0–65	15.9	± 13.0
Severity	26	0–154	35.3	± 32.9

1 day. Cortisol data were natural log transformed for analysis. Extreme outliers (> 3 SD + mean) were excluded from the analysis ($n = 5$ samples). Samples collected more than 45 min after T1 were excluded ($n = 1$), leaving 814 samples for analysis. The CAR, diurnal cortisol slope, and area under the curve (AUC) (Pruessner et al. 2003) were calculated from

the transformed values for each of the 3 days and averaged. The CAR represents the normal rise in cortisol after waking which is thought to help facilitate alertness and energy mobilization for the day ahead. The diurnal slope represents the degree to which cortisol levels decline over the course of the day. The AUC is an estimate of total daily cortisol exposure.

Stress and Adversity Inventory

The Stress and Adversity Inventory (STRAIN) is an online instrument that assesses an individual's cumulative exposure to stress over the life course, measuring exposure to 96 lifetime stressors (Slavich and Epel 2010). Each stressor is followed by questions regarding the frequency, timing, duration, and perceived severity of the stressor. Thus, summary scores across multiple dimensions of lifetime stress can be examined including indices (objective vs. subjective), timing (early life < 18 years vs. adulthood > 18 years), type (chronic vs. acute), life domain (e.g., housing, work), and social-psychological characteristic (interpersonal loss, physical danger, etc.). The instrument has established concurrent validity with the Childhood Trauma Questionnaire. The STRAIN has also demonstrated predictive validity for a variety of health-related and cognitive outcomes, and excellent test-retest reliability ($r = .919$, $p < .001$) (Slavich and Shields 2018). For the purposes of this analysis, we analyzed objective data (i.e., counts of exposure) categorized by timing (early life vs. adulthood). Scores for ELA and adulthood adversity were based on continuous counts, with higher counts indicating greater exposure to adversity. The ELA and adulthood adversity variables capture a wide variety of stressors that can occur in childhood and/or adulthood, including maltreatment (e.g., harsh parenting, parental substance use, emotional, sexual and physical abuse), along with other non-maltreatment types of adversity (e.g., homelessness, overcrowded housing, school drop-out, hospitalizations).

Depressive symptoms

The Edinburgh Depression Scale (EDS) is a 10-item self-report scale measuring depressive symptoms over the last 7 days, rated on a 4-point scale from zero (no, not at all) to three (yes, most of the time) (Cox et al. 1987). Although originally developed for use in postpartum women, the EDS tool has since been validated for use in pregnant women (Bergink et al. 2011). The scale purposively omits somatic symptoms that overlap with pregnancy, including fatigue, and changes in eating and sleeping patterns. Summed scores range from 0 to 30, with higher scores indicating greater severity of depressive symptoms. Internal consistency reliability was $\alpha = .84$ in this study. Test-retest reliability ($r = .63$), concurrent validity, and predictive criterion validity have previously been established (Cox et al. 1987; Bergink et al. 2011). A score of 10 or greater has been recommended as the cutoff for women in the second trimester of pregnancy based on the combined metrics of sensitivity (70%), specificity (96%), and positive predictive value (39%) (Bergink et al. 2011). Thus, we created a dichotomized variable for elevated depressive symptoms (high ≥ 10; $n = 16$). While not diagnostically indicative, a score ≥ 10 represents a broader category inclusive of mild or emerging symptoms. Clinically, the EDS is frequently utilized in primary care obstetric clinics to identify women for further assessment, treatment, or preventative depression interventions.

Statistical analysis

Confounding covariates were systematically identified. First, correlations to the predictor/outcome variables were screened across 30 possible confounding variables, including sociodemographic (e.g., race, income, education) and pregnancy-related variables (e.g., body mass index, pregnancy weight gain, fetal sex, infection). Variables that demonstrated significant correlations to both the predictor and outcome variables were then included in a step-wise linear regression for each cortisol parameter separately. Only age and smoking were consistently indicated as potentially significant confounding variables that should be included in the final models.

The Spearman correlations, analysis of variance (ANOVA), and the Mann-Whitney U tests were used to determine the associations between ELA, adulthood adversity, depressive symptoms, sociodemographic variables, and cortisol. The interval of time (hours) between T1 and T5 was controlled for in analyses involving AUC. Gestational time point at cortisol collection and average time at awakening were not correlated with the cortisol parameters and thus were not included as covariates in analyses. The variables of ELA and adulthood adversity were mean-centered to reduce non-essential multicollinearity. Since adulthood adversity exposures were analyzed based on count (rather than duration of exposures), scores were not directly amplified as a function of having spent more time as an adult. In fact, there was a strong, negative correlation between adulthood adversity and age ($\rho = -.58$, $p < .01$), indicating that younger women experienced more adulthood adversity, despite their relatively shorter duration of time as an adult.

Multiple linear regression was performed to model ELA, adulthood adversity, and depressive symptoms in predicting averaged log transformed cortisol parameters (CAR, slope, AUC). The confounds of age and smoking were entered first (model 1), followed by the main effects of ELA, adulthood adversity, and depressive symptoms (model 2). Interaction terms ELA × adulthood adversity and ELA × depressive symptoms were added separately (models 3 and 4) to assess moderating effects of ELA. Since significant correlations were expected among the predictor variables, we examined statistical indicators of multicollinearity (tolerance and the variance inflation factor [VIF]). These values were within recommended limits (tolerance > .1; VIF < 10). Statistical significance was set at $p = .05$.

Results

Preliminary associations

Mean cortisol parameters are listed in Table 1. Correlations between cortisol and study variables are shown in Table 2. Female fetal sex was associated with significantly higher awakening cortisol ($t = -2.30$, $df = 52$, $p = .03$), contributing to a blunted CAR ($t = 2.50$, $df = 52$, $p = .02$) and steeper slope ($t = 2.17$, $df = 52$, $p = .04$). Prenatal infection (combined index of bacterial vaginosis, yeast infection, urinary tract infection, sexually transmitted infection) was associated with significantly higher mean adulthood adversity score. Despite these associations, neither fetal sex nor prenatal infection were significantly associated with both the predictor and outcome variables. Thus, we did not include these as confounders. Women scoring in the upper 25th percentile for adulthood adversity were 2.5 times more likely to experience a prenatal infection (chi-squared 10.9, $p = .01$). However, mean cortisol levels did not differ by infection status, likely due to early detection and treatment in early pregnancy (i.e., well before our cortisol sampling in the late second trimester). Parity, body mass index, and total prenatal weight gain were not significantly correlated with any of the main predictors or cortisol parameters (all p values > .10). With regard to sociodemographic factors, age was most consistently indicated for inclusion as a confounding variable. Young age at the time of pregnancy was correlated with greater previous exposure to early life and adulthood adversity, as well as some cortisol parameters. During pregnancy, maternal age appeared to serve as a concise proxy for a host of sociodemographic variables. In our sample, younger women had less education and income and were more likely to be women of color and single.

Higher total life adversity was significantly correlated with higher cortisol at T2 ($\rho = .27$, $p = .04$), which was primarily accounted for by ELA ($\rho = .36$, $p = .01$), rather than adulthood adversity. Adulthood adversity did not significantly correlate with any cortisol parameters, even after adjusting for participants' length of time as an adult. Women with elevated depressive symptoms had significantly higher cortisol at awakening (T1) [F (1, 56) = 10.2, $p < .01$], in the evening (T4) [F (1, 56) = 7.1, $p = .01$], and at bedtime (T5) [F (1, 56) = 10.3, $p < .01$]. Women with elevated depressive symptoms also had a significantly blunted CAR [F (1, 56) = 6.3, $p = .02$] and higher AUC [F (1, 56) = 7.8, $p < .01$].

Direct effects

In the regressions, both ELA and depressive symptoms significantly predicted CAR as direct effects after adjusting for age and smoking, explaining 28% of the variance in CAR (Table 3). Depressive symptoms were associated with a

Table 2 Bivariate Spearman's correlations between sample demographic characteristics and main study variables ($N = 58$

	T1	T2	T3	T4	T5	CAR	Slope	AUC	ELA	Adulthood adversity	Depressive symptoms
Saliva log variables											
Prior night sleep duration	−.08	−.21**	.09	−.01	−.13	−.11	−.07	−.22*	.03	.03	−.21
Daily stress rating	.24**	.12	−.03	−.03	.12	−.13	−.18*	.09	.28*	.20	.12
Mean wakeup time	.13	.08	−.02	−.10	−.04	−.06	.06	.41**	.08	.05	.14
Psychosocial and demographic characteristics											
Age	.14	.22	−.06	−.16	−.26	.22	−.28*	−.14	−.28*	−.58**	−.22
Education	.15	.08	−.04	−.16	−.16	<.01	−.27*	−.05	−.32*	−.22	−.14
Income	.14	.20	−.02	−.14	−.20	.07	−.27*	−.03	−.25	−.35*	−.34*
Prenatal distress	.10	−.06	.05	.08	.01	−.15	−.05	.12	.05	.10	.46**
Birth outcomes											
Length of gestation	−.18	.05	−.06	.04	−.05	.19	0.16	.01	.03	−.04	−.25
Birth weight	−.09	.11	−.06	−.01	−.05	.29*	.02	−.06	−.17	−.24	−.14
Birth length	.08	.15	−.06	−.01	.07	.11	.06	.02	−.20	−.31*	−.04
STRAIN											
Total life adversity	.00	.27*	.02	.18	.20	.21	.10	.14	–	–	.44**
Early life adversity	.07	.36**	.12	.13	.02	.18	−.05	.10	–	.50**	.27*
Adulthood adversity	−.07	.04	−.02	.16	.25	−.01	.18	.13	.50**	–	.42**

T1 awakening, *T2* awakening + 30 min, *T3* midday, *T4* evening, *T5* bedtime, *CAR* cortisol awakening response, *slope* diurnal slope from T1 to T5 adjusted to per hour, *AUC* area under the curve (excluding T2), *ELA* early life adversity

*Significant at the $p < .05$ level; **significant at the $p < .01$ level

Table 3 Multiple linear regression examining confounders, main effects, and interactions for cortisol parameters

	Cortisol awakening response (CAR)				Diurnal cortisol slope				Cortisol area under the curve (AUC)			
	Beta	*t*	*p*	Adjusted R^2	Beta	*t*	*p*	Adjusted R^2	Beta	*t*	*p*	Adjusted R^2
Confounding variables				.03				.08*				.21**
Age	.12	.89	.38		− .28	− 2.16	.04		− .10	− .83	.41	
Smoking	− .23	− 1.72	.09		.20	1.54	.13		.04	.31	.76	
Length of day	–	–	–		–	–	–		.48	4.01	< .01	
Main effects				.28**				.12*				.25**
Early life adversity (ELA)	.44	3.44	< .01		.01	.08	.94		0.09	0.64	.52	
Adulthood adversity	.18	1.21	.23		.00	− .02	.98		− .01	− .03	.98	
Depressive Symptoms[a]	− .40	− 2.81	.01		− .35	− 2.27	.03		0.29	2.09	.04	
Interactions[b]												
ELA × adulthood adversity	− .29	− 2.60	.01	.35**	− .35	− 2.89	.01	.23**	− .10	− .82	.42	.25**[c]
ELA × depressive symptoms	− .06	− .46	.65	.27**[c]	− .42	− 2.96	< .01	.24**	− .09	− .60	.55	.24**[c]

*$p < .05$; **$p < .01$

[a] ≥ 10 on Edinburgh Depression Scale

[b] Interactions were added separately, one model for each term

[c] No significant change in R^2 with addition of interaction term

blunted CAR ($\beta = -.40$, $p = .01$), whereas ELA was associated with a larger CAR ($\beta = .44$, $p \leq .01$). In order to better illustrate these differences, Fig. 1a, b depicts the sample subdivided into four groups based on levels of ELA and depressive symptoms: (1) ELA only ($n = 8$), (2) depressive symptoms only ($n = 7$), (3) depressive symptoms + ELA ($n = 9$), and (4) a reference group with few to no depressive symptoms and low ELA ($n = 33$). The sub-groups had noticeably divergent cortisol parameters and trajectories over the course of the day. Table 4 summarizes mean group differences in cortisol at each sampling time point, as well as differences in demographic characteristics, ELA, adulthood adversity, and depressive symptoms.

Depressive symptoms were a significant predictor of higher cortisol AUC in regression analyses while controlling for age, smoking, and time since awakening (Table 3). This model explained 25% of the variance in AUC. There were no significant predictors of diurnal slope.

Moderating effects

ELA moderated adulthood adversity in predicting CAR. Greater adulthood adversity predicted a blunted CAR, but only in women with high ELA (Fig. 2a). This interaction effect was primarily accounted for by higher awakening (T1) cortisol in women with ELA and depressive symptoms. ELA also moderated depressive symptoms in predicting cortisol slope (Fig. 2b). As depressive symptoms increased, the diurnal cortisol slope of women with low ELA became flatter, while the diurnal cortisol slope of women with high ELA became steeper. This interaction pattern was also found for ELA × adulthood adversity. ELA did not moderate main effects of adulthood adversity or depressive symptoms on AUC.

Discussion

These findings give support to theories that early life is an important critical window of development during which adverse environmental contexts may program long-term alterations in the HPA system that persist into adulthood. We found that higher exposure to adversity early in life, but not during adulthood, was associated with a larger CAR. This finding is congruent with results from other recent studies examining the relationship between ELA and cortisol during pregnancy (Thomas et al. 2018b). In a similar study using the STRAIN with pregnant women, Gillespie et al. (2017) found that higher plasma cortisol was associated with greater levels of ELA, but not adulthood adversity. Our finding that ELA was associated with a larger CAR is in line with the findings of other recent studies (Bublitz and Stroud 2012; Thomas et al. 2018a). This finding is notable given that pregnancy is typically associated with a smaller CAR as gestation advances (Entringer et al. 2010). In addition to corroborating the findings of recent studies, our research contributes new knowledge suggesting that early adversity moderates the effects of both adulthood adversity and prenatal depressive symptoms on HPA function.

Depressive symptoms were associated with a blunted CAR, which is consistent with meta-analysis findings in pregnant (Seth et al. 2016) and non-pregnant women (Stetler and Miller 2005). In contrast, a few studies have found that depression is associated with a larger CAR in pregnant and non-

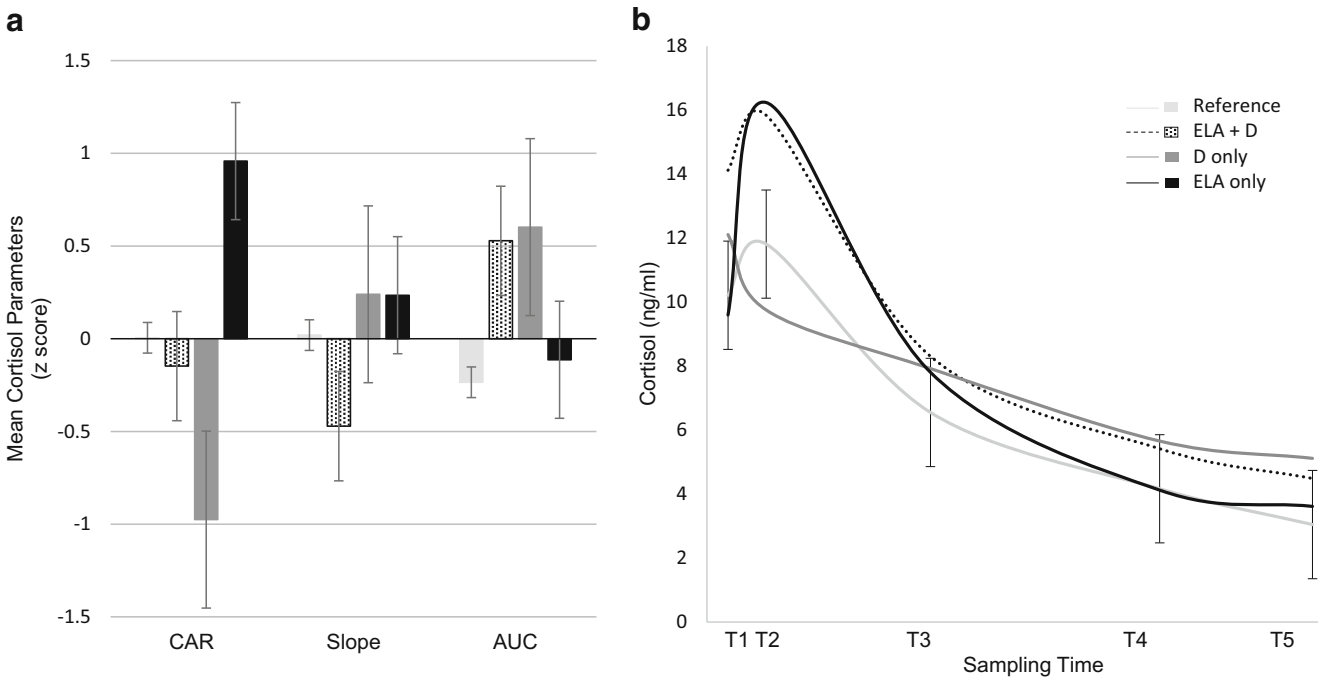

Fig. 1 **a** Mean cortisol parameters converted to a *z*-score and compared between groups. Error bars = standard error. **b** Line graphs of diurnal cortisol trajectory among sub-groups. High ELA is defined as ≥ 1 SD above the mean, equivalent to 6 or more childhood events or chronic difficulties before 18 years of age. Depressive symptoms (D) was defined as ≥ 10 on the Edinburgh Depression Scale. The reference group consists of women who scored low on both depressive symptoms and ELA measures. Error bars = standard error of the reference group mean; cortisol represents raw, non-transformed values. D depressive symptoms; T1 awakening; T2 awakening + 30 min; T3 midday; T4 evening; T5 bedtime

pregnant samples (Vreeburg et al. 2009; O'Connor et al. 2014). Our findings suggest that mixed results could be due to unaccounted differences in women's history of ELA. In our study, women with both high ELA and high depressive symptoms had a mean CAR that was comparable to the reference group. One explanation for this finding is that an additive overlap occurs, such that the amplifying effects (positive regression coefficient) and blunting effects (negative regression coefficient) on the CAR overlap to produce what appears to be a typical CAR in women with both ELA and depressive symptoms (Fig. 1a). This is despite differing overall diurnal cortisol trajectories between these groups (Fig. 1b).

This finding is notable given that women who experience ELA have significantly greater odds of experiencing an episode of depression in adulthood (Chapman et al. 2004; Records and Rice 2009) with trajectories of chronic, recurrent depression that are less likely to respond or remit to medication, therapy, or both (Nanni et al. 2012). ELA has also been associated with poor health behaviors such as greater rates of smoking, alcohol, and illicit drug use, and lower rates of physical activity (Felitti et al. 1998) all of which could influence cortisol regulation, as well as compound unfavorable physical, mental, and reproductive health outcomes for women during pregnancy (McDonnell and Valentino 2016). The interactive effects of these factors need to be examined in future research.

In addition to blunting effects on the CAR, we found that depressive symptoms predicted higher total basal cortisol across the day (i.e., AUC) among women with high depressive symptoms. The findings of elevated evening (T4) and bedtime (T5) cortisol are consistent with previous findings of elevated cortisol in depressed pregnant women (Iliadis et al. 2015) and non-pregnant individuals (Vreeburg et al. 2009).

In support of our findings, prior studies have shown ELA to be an important moderator of HPA stress reactivity in depressed women resulting in distinct sub-types of depression with unique HPA phenotypes (Heim et al. 2008). In a recent study examining the interaction of depression and ELA on CAR in a non-pregnant sample, individuals with ELA, regardless of depression, were similarly found to have a larger CAR (Lu et al. 2016). Furthermore, only individuals with both ELA and depression showed decreased glucocorticoid feedback inhibition (i.e., higher cortisol) in response to a dexamethasone suppression test (Lu et al. 2016). In combination with our findings, these results suggest depressive HPA phenotypes based on ELA. Our findings demonstrate such a phenotype for the first time in pregnant women.

Another key finding of our research was that ELA moderated the relationship between adulthood adversity and depressive symptoms on cortisol. Women with high ELA had increasingly smaller CAR as adulthood adversity increased. Since greater stress and adversity are associated with higher incidence of depression, this finding could represent an artifact of a blunted CAR characteristic of depression. Women

Table 4 Comparison of sub-group means by early life adversity (ELA) and depressive symptoms

	Reference	ELA + depressive symptoms	Depressive symptoms only	ELA only
Cortisol (Ln transformed)				
T1: awakening	2.32	2.66**	2.51	2.30
T2: awake + 30 min	2.46	2.76*	2.32	2.73*
T3: midday	1.94	2.12	2.12	2.06
T4: evening	1.56	1.80*	1.80	1.56
T5: bedtime	1.33	1.54*	1.63*	1.38
CAR	.14	.09	− .17*	.44*
Slope	− .06	− .08	− .06	− .06
AUC	1637.12	1860.10	1881.62	1672.60
Demographics				
Income[a]	3.59	1.25*	1.14*	1.71
Education[b]	5.03	3.89*	4.14	3.71*
Age	29.46	24.49*	27.00	26.94
Adversity				
ELA count	1.67	9.78**	2.00	13.13*
Adulthood adversity count	10.73	28.89*	21.86	17.75*
Depressive symptom score	4.42	13.44**	12.86**	5.63

Comparison to the reference group using the Mann-Whitney test

*$p < .05$; **$p < .01$

[a] Annual household income levels: (1) $10–20,000; (2) 20–39,000; (3) > $40,000

[b] Education levels: (1) 8th grade; (2) less than high school; (3) completed high school; (4) some college; (5) college degree

with high ELA also had steeper diurnal cortisol slope as depressive symptoms and adulthood adversity increased. Both of these moderating effects were driven by higher awakening (T1) cortisol in women with elevated depressive symptoms and higher adulthood adversity, but particularly so for women with ELA (see Fig. 1b). Similarly, Bublitz and Stroud (2013) reported evidence of prior day stress being associated with higher morning cortisol in women, but only those who experienced prior childhood sexual abuse. Seng et al. (2018) also reported higher morning cortisol in pregnant women with dissociative symptoms related to early trauma. Higher T1, in general, may be a result of reduced ability to make fine-tune adjustments in pre-awakening adrenal sensitivity (Clow et al. 2004). Glucocorticoid resistance is another a widely discussed explanatory mechanism for depression-related elevations in cortisol, particularly for individuals who have experienced ELA (Pariante and Lightman 2008).

While a larger CAR could represent higher cortisol reactivity, it also could represent a higher threshold required to facilitate awakening (e.g., alertness and energy mobilization). In this case, our finding of larger CAR (but not basal cortisol levels) in women with ELA would support the idea that ELA is associated with a higher threshold for cortisol response. While a higher threshold may render the stress response resistant to non- or low-stress conditions (an advantage), it may likewise render more resistance towards experiencing the small, day-to-day feelings of reward and joy. For now, this explanation remains speculative and should be tested through additional research. However, the implications could be important for understanding risk for cortisol dysregulation in pregnant women. This would be especially relevant for women with ELA who are at highest risk for chronic and treatment-resistant trajectories of depressive illness and poor pregnancy/parenting outcomes. Awareness of ELA may help clinicians identify those who may benefit from close monitoring for depressive symptoms so that timely treatment or referral to psychiatric providers can be initiated.

It is also important to note that there was a relatively high prevalence of women scoring above the cutoff for depressive symptoms in this study (28%) compared to what has previously been reported (12.8%) (Bennett et al. 2004). There are two possible explanations for this finding. First, among the sub-group of Black pregnant women in our study, 46% scored above cutoff, compared to only 14% of White/Caucasian women in the study. This difference may be related to high rates of poverty among Black women in this particular community. The relatively low representation of racial minority women in prior studies may have produced underestimates of depression prevalence, especially among women exposed to greater life course adversity. Additionally, the use of 10 as a cutoff value for the EDS is somewhat lower than has been used in prior studies of pregnant women (e.g., ≥ 13 on the EDS). Nonetheless, the higher rate of depressive symptoms for Black women in our sample highlights the importance of

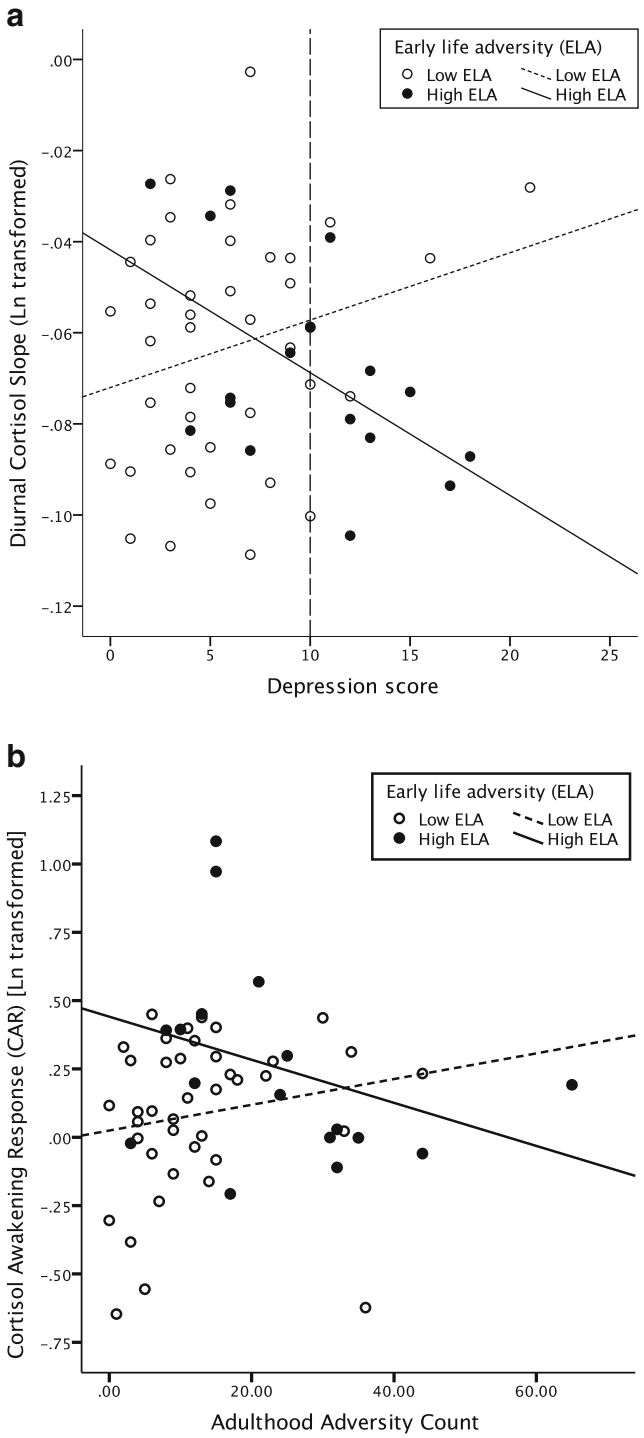

Fig. 2 **a** Interaction plot illustrating the moderating effect of early life adversity (ELA) on the relationship between depressive symptoms and diurnal cortisol slope. Vertical line = depressive symptom cutoff of ≥ 10 on the Edinburgh Depression Scale. Low ELA: R^2 linear = 0.064; high ELA: R^2 linear = 0.294. **b** Interaction plot illustrating the moderating effect of early life adversity (ELA) on the relationship between adulthood adversity and cortisol awakening response. Low ELA: R^2 linear = 0.029; high ELA: R^2 linear = 0.111

clinician attention to social determinants of health (e.g., income, housing, food availability, social support) and referral to resources that support maternal-child health during perinatal care.

Limitations

Limitations of this study include a cross-sectional, descriptive, one-group design which precludes making conclusions about causality or changes over time. The study relied on participants to accurately collect their own saliva without objective tracking (e.g., use of MEMS® caps). The study was also limited by a small sample size. As a result, our analyses controlled for a limited number of the most important confounding variables. For instance, the quality and duration of sleep were not included in model testing because they were not significantly related to both predictors and dependent variables. However, they could have confounding effects on the relationship between depressive symptoms and specific cortisol indices. In addition, the study did not utilize a diagnostic measure of depression. Therefore, the findings speak to a broader category of elevated depressive symptoms, rather than diagnosed major depressive disorder. Clinically, the EDS is used in primary care obstetric settings as a method to identify women for targeted/preventative interventions for depressive symptoms. Therefore, the measure reflects what is clinically feasible in a primary care obstetric setting.

Conclusion

This study is one of the first to examine life course adversity and depressive symptoms concurrently in pregnant women. These preliminary findings suggest that ELA and depressive symptoms differentially predicted cortisol in pregnant women and that ELA moderated the relationships of both current depressive symptoms and more proximal adulthood adversity to cortisol parameters. Findings provide preliminary evidence that women's exposure to early adversity may program the HPA system to produce lasting changes in cortisol regulation. Clinically, these findings contribute to a broader scientific discussion on whether differences in HPA functioning during pregnancy underlie differential birth outcomes, as well as variation in depressive symptom trajectories or depression treatment response. Our results suggest that women who experience early adversity are potentially at greatest risk for cortisol dysregulation and more severe depressive symptoms. Prenatal visits offer a window of opportunity for assessing a woman's exposure to adversity early in her life and referral for a more comprehensive psychiatric evaluation if warranted. Trauma-informed interventions during pregnancy may reduce the likelihood of adverse birth outcomes and development of clinical depression during the perinatal or postpartum periods. Future

research could examine the value of such interventions. In addition, further research is needed to replicate our results with larger samples of diverse women.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board affiliated with the recruitment site and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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