Published in final edited form as:

Stress. 2019 January ; 22(1): 53–59. doi:10.1080/10253890.2018.1501023.

Maternal circadian cortisol mediates the link between prenatal distress and breastfeeding

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Abstract

Breastfeeding is associated with positive maternal and infant outcomes. It is recommended that women exclusively breastfeed for the first six months postpartum, however these recommendations are not met in the majority of women. Psychological distress in pregnancy is associated with lower rates of breastfeeding initiation and duration in the postpartum period. The mechanisms linking maternal distress to breastfeeding are not understood. In this study we examined maternal circadian cortisol as a mechanism linking distress in pregnancy to breastfeeding. This study is a secondary data analysis of 197 pregnant women with singleton pregnancies who were part of a larger study of the effects of maternal mood on fetal and infant development. Thirty-four percent of women reported exclusively breastfeeding, 18% reported exclusively formula feeding, and 48% reported mixed feeding. Participants reported on perceived stress, perinatal anxiety and depression, and socioeconomic status during pregnancy. They provided salivary cortisol samples at three times a day for three days at 24, 30, and 36 weeks' gestation. Participants who reported lower socioeconomic status in pregnancy were less likely to breastfeed, and lower maternal cortisol awakening responses mediated this association. This area of research may identify foci in the prenatal period that could serve as targets for interventions to increase rates of breastfeeding.

Lay Summary

Pregnant women who reported lower socioeconomic status in pregnancy were less likely to breastfeed. This association was mediated by lower cortisol awakening responses, but not evening cortisol levels, over pregnancy.

Keywords

Breastfeeding; stress; socioeconomic status; diurnal cortisol; cortisol awakening response; pregnancy

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Disclosure of Interest: The authors report no conflicts of interest.

Introduction

Breastfeeding is associated with reduced risk for obesity, diabetes, childhood leukemia, and sudden infant death syndrome (SIDS) in infants, and reduced risk for diabetes, breast, and ovarian cancers in mothers (Ip et al., 2007). In light of the associated health benefits for women and infants, the American Congress of Obstetricians and Gynecologists recommends that women exclusively breastfeed for at least the first six months after delivery and continue to breastfeed for a year and for as long as desired by mothers and infants. However, only 19% of women in the United States meet this recommendation (Bartick & Reinhold, 2010).

Past research has identified maternal demographic and psychosocial characteristics that predict initiation and duration of breastfeeding. Demographic characteristics include parity, maternal age, race/ethnicity, smoking, obesity, and experience with breastfeeding. Psychosocial characteristics associated with reduced initiation and duration of breastfeeding include symptoms of prenatal depression and anxiety (Ahlqvist-Bjorkroth et al., 2016; Lau, 2001; Whalen & Cramton, 2010), stressful life events in pregnancy (Li et al., 2008; Zhu et al., 2013), and lower socioeconomic status (Ertem et al., 2001; Thulier & Mercer, 2009; Wijndaele et al., 2009).

A mechanistic understanding of how prenatal psychosocial stressors impact breastfeeding behavior in the postpartum period is currently unknown. Mechanisms that have been proposed to underlie both psychosocial disturbances in pregnancy and difficulty breastfeeding include shifts in gonadal/placental steroids, lactogenic hormones, and hypothalamic-pituitary-adrenal (HPA) axis activity (Stuebe et al., 2012). Regarding HPA activity, the presence of the stress hormone cortisol (along with insulin and prolactin) is necessary for mammary secretory differentiation (when mammary epithelial cells differentiate into lactocytes (Pang & Hartmann, 2007)) and secretory activation (when lactose is present in mammary glands beginning about 30–40 hours after birth (Pang & Hartmann, 2007)). The first stage of mammary differentiation begins in mid-pregnancy (Neville et al., 2001). As parturition approaches, glucocorticoids bind to receptors in mammary cells and work synergistically with prolactin transcription factors to facilitate milk production (Pang & Hartmann, 2007). Given the robust association between psychosocial stress in pregnancy and maternal HPA activity (de Weerth & Buitelaar, 2005; Sandman et al., 1997), it is possible that psychosocial disturbances in pregnancy interrupt mammary secretory differentiation and activation via changes in maternal HPA activity, resulting in a decreased ability to breastfeed.

Despite the importance of glucocorticoids secretion on mammary development in pregnancy, no prior studies have examined maternal HPA activity as a mechanism linking psychosocial stress in pregnancy to breastfeeding. Therefore, in this study we aimed to examine if maternal circadian cortisol mediated the association between psychosocial stress in pregnancy and breastfeeding in the postpartum period. We hypothesized that the association between higher psychosocial stress and decreased likelihood to breastfeed would be mediated by HPA dysregulation. An improved understanding of the pathways linking maternal distress in pregnancy to breastfeeding is necessary for the effective development of interventions to promote breastfeeding in the postpartum period.

Methods

Participants

Participants were 197 pregnant women with singleton pregnancies whose breastfeeding status at one month after delivery was known and who were part of a larger study of the effects of maternal mood on fetal and infant development (*citation omitted for blind review*). Women were excluded from participating if they were < 18 or > 40 years old and if they were at risk for maternal or obstetric complications. Maternal and infant characteristics, categorized according to breastfeeding status, are presented in Table 1.

Thirty-four percent of women reported exclusively breastfeeding in the first month after delivery, 18% reported exclusively formula feeding, and 48% reported some combination of both breast and formula feeding (“mixed feeding”). Women in the current study were on average 27 years old ($SD=6$), from racially and ethnically diverse backgrounds (45% non-Hispanic White, 17% non-Hispanic Black, 26% Hispanic, 6% > 1 race, 4% Asian, 1% ‘other’, 1% American Indian), 43% were married, 46% of pregnancies were planned, 37% had a high school education or less, and 17% of the sample reported an annual income of less than \$10,000 USD. 34% of the sample was categorized as ‘low’ SES according to the Hollingshead Four Factor Scale. Infants were born on average at 39 weeks gestation ($SD=2$), average weight was 3341 grams ($SD=542$), and APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score at 5 minutes after delivery was 9 ($SD=1$) demonstrating good health among infants born in this sample. The Institutional Review Boards of two hospitals approved this study. All women provided written consent prior to their participation. Research was conducted in an ethical and responsible manner, and is in full compliance with all relevant codes of experimentation and legislation.

Procedure

Pregnant women were interviewed 1–3 times during pregnancy (Session 1: 24 ($SD=3$) weeks; Session 2: 30 ($SD=1$) weeks; Session 3: 36 ($SD=1$) weeks) and one time in the postpartum period (approximately 30 days after delivery). 100% of participants completed at least 1 study interview, 81% completed at least 2 study interviews, 72% completed all three pregnancy interviews, and approximately 85% completed the postpartum interview. At the baseline interview, participants provided information on maternal characteristics (including socioeconomic status) and pregnancy health information. At each study session participants reported on symptoms of stress, depression, and anxiety in pregnancy. For three days following each interview, participants provided saliva samples (passive drool) upon awakening, 30 minutes after wake-up, and bedtime. After participants completed the 3 days of saliva collection, study staff retrieved samples from participants’ homes and provided payment.

Measures

Breastfeeding Status.—At approximately one month after delivery, participants were asked to report their breastfeeding status. Women were then categorized into three groups: those who reported exclusively breastfeeding for the first month after delivery, those who reported exclusively formula feeding for the first month after delivery, and those who did a

mix of breast and formula feeding. At each interview in pregnancy, participants were asked about their intentions to breastfeed using the following question: “How are you planning on feeding your baby?” Response options were breastfeed only, breast and formula feed, formula feed only, not sure, and refused to answer.

Maternal cortisol.—Up to 36 saliva samples were collected from each participant throughout the study and returned to the lab by study staff, aliquoted, and stored at -80°C until analysis. Samples were then shipped to the laboratory of Clemens Kirschbaum, Ph.D. (Dresden University). Cortisol concentrations were analyzed with an immunoassay with time-resolved fluorescence detection. The intra and inter-assay coefficients of variation were $< 8\%$. A subset of the sample (17%) were given Medication Event Monitoring System (MEMS) caps (AARDEX, Zurich, Switzerland) that time stamp every opening of bottles containing tubes used to collect maternal saliva. For participants with both self-reported and MEMS-recorded saliva sampling times, there was an average time discrepancy of 8 minutes ($\text{SD}=5$) suggesting that, in a subset of participants, women were adherent to the sampling protocol.

Maternal and infant conditions.—Maternal medical conditions were assessed via chart review at enrollment and following delivery. Medical conditions included diagnosis of gestational diabetes mellitus (GDM), preeclampsia, and hypertension. Infant outcomes, including gestational age at birth, birth weight, and APGAR score at 5 minutes after delivery, were collected from medical chart review following delivery.

Socioeconomic Status (SES).—Participants were asked to self-report the current occupation and highest level of education for themselves and another contributing adult at their first study session. To measure SES we utilized the Hollingshead Four Factor Scale (Hollingshead, 1975). This measure is an index of SES based on weighted scores of education and occupation of contributing adults. Occupations were coded according to the Hollingshead Four Factor occupational codes. Hollingshead scores range from 1–5, with scores of 4 and 5 indicating low SES. Scores were categorized into ‘low’ (scores 4 and 5) and ‘high’ (scores 1–3). The Hollingshead measure is one of the most frequently used measures of socioeconomic position and has demonstrated good inter rater reliability in past research (Cirino et al., 2002).

Maternal Depressive Symptoms.—At each study session, pregnant mothers reported their depressive symptoms using the Quick Inventory for Depressive Symptomatology (QIDS) (Rush et al., 1986). The QIDS is a 16-item measure designed to assess depressive symptom severity in the past 7 days. The QIDS has demonstrated acceptable psychometric properties in depressed patients (Rush, et al., 1986). Scores on the QIDS range from 0 to 27, with scores > 15 indicating severe symptoms of depression.

Maternal Anxiety Symptoms.—Maternal anxiety symptoms were measured by asking women to rate the severity of symptoms across 14 items that measure mental agitation, psychological distress, and somatic anxiety. Response options range from 0=not present to 4=very severe. Scores > 24 indicate severe symptoms (Hamilton, 1959).

Maternal Perceived Stress.—The perceived stress scale is a 10-item self-report measure that asks participants to report the degree to which they perceived situations as stressful over the past month on a scale of 0=never to 4=very often. Higher scores reflect greater stress (Cohen et al., 1983).

Statistical Approach

Cortisol data reduction.—We calculated the cortisol awakening response (CAR) (Clow et al., 2004) on each day of saliva collection by taking the difference between cortisol values upon awakening and 30 minutes after wake-up and then averaging CAR across the three days of collection. Morning saliva samples that were < 20 or > 40 minutes apart were omitted from analyses in order to accurately capture the cortisol awakening response. Valid maternal cortisol data was available for 163 women at the first interview, 176 women at the second interview, and 170 women at the third interview. CAR and evening cortisol are regulated by different biological processes (Wilhelm et al., 2007) and thus were analyzed separately. CAR and evening cortisol values were log transformed due to skewed distributions. Raw values are presented in figures.

Hypothesis testing.—To assess the influence of potential covariates, we performed one-way analysis of variance (ANOVA) and chi-squared analyses to examine differences in maternal and infant characteristics by the three breastfeeding groups (formula feeding, breastfeeding, mixed feeding). Characteristics that differed by breastfeeding group were included as covariates in subsequent analyses. Repeated measures analysis of covariance (ANCOVA) were performed to assess if maternal cortisol values over pregnancy differed by breastfeeding groups. Multinomial logistic regression analyses were performed to examine if indices of maternal distress predicted breastfeeding group, and if maternal cortisol mediated the association between maternal stress and breastfeeding.

Results

Breastfeeding groups significantly differed on a number of psychosocial characteristics including pre-pregnancy body mass index ($F(2,186)=5.79, p=.004$), maternal age ($F(2,194)=18.08, p<.001$), marital status ($\chi^2=31.57, p<.001, df=2$), and race/ethnicity ($\chi^2=9.11, p=.01, df=2$). Women who reported formula feeding in the first month after delivery were significantly younger and had higher body mass index prior to pregnancy. Women who breastfed were more likely to be Caucasian. Breastfeeding groups did not significantly differ on maternal medical conditions (gestational diabetes mellitus, hypertension, or preeclampsia) (p values > .23), parity ($p=.18$), delivery mode ($p=.75$), or postpartum depression ($p=.42$). Groups did not significantly differ on infant outcomes including gestational age at birth, small for gestational age, and APGAR scores five minutes after delivery (p values > .10). Pre-pregnancy BMI, maternal age, and race/ethnicity were included as covariates in subsequent analyses.

Breastfeeding and maternal distress in pregnancy

A multinomial logistic regression was performed to model the relationship between maternal distress in pregnancy (depression, anxiety, stress, SES) and membership in the three

breastfeeding groups (breastfeeding, formula feeding, or mixed). After adjusting for maternal age, race, and pre-pregnancy BMI, results indicated that the addition of SES ($\chi^2=10.29$, $p=.006$, $df=2$) significantly improved the fit between model and data. The reference group was breastfeeding. Pregnant women who reported lower SES were more likely to formula feeding ($\beta=-2.03$, $SE=.67$, $p=.002$) and mixed feeding ($\beta=-1.20$, $SE=.57$, $p=.04$) than breastfeed. Breastfeeding group membership did not differ by perceived stress, depression, or anxiety symptoms in pregnancy (p values $> .22$).

SES and cortisol in pregnancy

We next examined if maternal SES in pregnancy was associated with maternal cortisol by performing multivariate analysis of variance. After adjusting for significant covariates, we found that SES was significantly associated with CAR at 30 weeks ($\beta =3.96$, $p=.05$) and was marginally associated with evening cortisol at 24 ($\beta =3.06$, $p=.08$) and 36 weeks ($\beta =3.42$, $p=.07$). Women who reported lower SES displayed lower CAR and marginally higher evening cortisol, representing a flattening of the diurnal rhythm across pregnancy among lower SES pregnant women.

Breastfeeding and Cortisol in Pregnancy

Results from repeated measures analysis of covariance revealed a main effect of breastfeeding group on maternal CAR across pregnancy ($F(2)=4.29$, $p=.02$). Tukey's post hoc comparison revealed that women who formula fed had significantly lower CAR over pregnancy compared those who mixed fed ($p=.03$). We did not find evidence of a main effect of breastfeeding group differences in evening cortisol in pregnancy ($F(2)=1.13$, $p=.33$). Univariate analysis of covariance revealed that differences were significant at 24 weeks' gestation ($F=6.45$, $p=.002$). Post hoc paired comparisons indicated that cortisol awakening responses were significantly lower among women who formula fed compared to those who mixed fed ($p=.03$). We did not observe significant differences in cortisol awakening responses by breastfeeding group at 30 weeks' gestation ($F=2.62$, $p=.08$) or at 36 weeks' gestation ($F=5.78$, $p=.35$).

Cortisol as a mediator between maternal distress and breastfeeding

Given the significant associations between SES and CAR, and breastfeeding group and CAR, we examined maternal CAR in pregnancy as a mediator in the association between maternal SES and breastfeeding group membership by performing multinomial logistic regression. Breastfeeding was again the reference group. We found that, after adjusting for CAR at 24, 30, and 36 weeks' gestation, SES no longer predicted breastfeeding group membership. Specifically, after adjusting for CAR there were no differences in formula feeding ($\beta=-.93$, $SE=.97$, $p=.40$) or mixed feeding ($\beta=-1.02$, $SE=.76$, $p=.36$) by maternal SES.

Discussion

Results from this study indicated that women who report low SES in pregnancy are less likely to breastfeed in the postpartum period. The association between SES and breastfeeding was mediated by maternal CAR over pregnancy. These findings are consistent

with prior research indicating an association between low SES in pregnancy and reductions in breastfeeding. Findings are also in line with past evidence that glucocorticoids in mid-gestation are necessary for mammary differentiation, activation, and milk production. Results from this study extend our understanding of maternal HPA activity as a mechanism in the association between maternal distress in pregnancy and breastfeeding behavior in the postpartum period.

We can articulate several possible explanations for study findings. We speculate that lower CAR observed in women with low SES may have interfered with mammary secretory differentiation that precedes secretory activation and milk production. Others have also proposed that there may be common neuroendocrine pathways between perinatal stress and breastfeeding (Stuebe, et al., 2012). Past research has found that hormonal shifts necessary for secretory differentiation, including maternal glucocorticoid production, begin as early as 20 weeks' gestation. Thus, lower CARs observed among women who reported low SES may have been insufficient for mammary epithelial cells to differentiate into lactocytes, potentially resulting in breastfeeding difficulty and greater rates of formula feeding in the first month postpartum.

Conversely, CARs were highest over pregnancy among women who mixed fed. Elevated CARs may have provided levels of glucocorticoids necessary for mammary differentiation and activation. Alternatively, elevated CAR may represent maternal HPA dysregulation, leading to difficulties with breastfeeding (particularly among women who did some degree of formula feeding). Past research suggests that CARs that fail to decline over pregnancy are associated with adverse pregnancy outcomes including shortened gestational length (Buss et al., 2009). Therefore, results from this study suggest that both low and high awakening responses may indicate HPA dysregulation and negatively affect breastfeeding success in the postpartum period. However, the mechanisms through which elevated maternal cortisol would impact mammary secretory differentiation and activation are unclear, and we do not yet understand if there is an 'ideal' cortisol levels are to promote breastfeeding success.

In contrast to previous studies, we did not observe associations between maternal symptoms of depression, anxiety, or perceived stress and breastfeeding. The lack of an association may have been due to the acuity of symptoms, as women were asked to report on mental health symptoms within the past week to one month. The observed association between low SES and breastfeeding could have been due to the chronicity of low SES, which likely pre-dated pregnancy and continued into the postpartum period, which may have influences maternal HPA activity. Consistent with our findings, past research indicates that chronic stressful life events in early pregnancy are associated with lower CAR (Obel et al., 2005), indicating that low SES in pregnancy may have resulted in blunted CAR and in turn disrupted mammary development. While we tested for a number of demographic characteristics that may have accounted for differences in breastfeeding, there are likely to be other un-measured sources of psychosocial stress or un-measured societal constraints (such as early return to work, paid maternity leave, accommodations for pumping breastmilk at work) that may have also contributed to both attenuated CAR and the likelihood of formula feeding. Future research is needed to address this limitation.

Cortisol awakening responses significantly differed by breastfeeding group, but evening cortisol levels did not significantly differ by group. Cortisol awakening response and evening cortisol are under different neuroregulatory control (Wilhelm, et al., 2007). The findings from this study suggest that neural regions that regulate the awakening response including the hippocampus and hypothalamic suprachiasmatic nucleus (Clow et al., 2010) may also be important in mammary secretory differentiation and activation. This has not yet been studied. However, evidence has demonstrated differences in patterns of maternal neural activation to infant cues among women who are breastfeeding vs. those who are not (Kim et al., 2011). More research is needed to understand the links between patterns of HPA diurnal rhythm and breastfeeding, as this area of research may reveal additional targets to increase breastfeeding.

Strengths of this study include multiple days of diurnal cortisol collection at multiple time points across pregnancy. Verification of cortisol collection times using electronic monitoring devices is another strength of the study. Results from this study should be interpreted in light of several limitations. Most notably, breastfeeding status was self-reported. We did not provide women with a definition of breastfeeding, and we do not have verification of breastfeeding or formula feeding behaviors. We also do not know if women had difficulty with breastfeeding, leading to an increased likelihood of formula feeding, or if they never intended to breastfeeding. This is an important limitation to address in future research, particularly given research indicating that low SES pregnant women may be less likely to decide on feeding choice until the end of pregnancy (Ertem, et al., 2001). In addition, women were followed until one month post-delivery. Longer-term follow up is necessary in order to assess the association between maternal distress, HPA activity in pregnancy, and the breastfeeding duration. Another limitation of this study is that we only collected salivary cortisol and did not measure other maternal hormones known to be associated with breastfeeding, such as oxytocin, prolactin, progesterone, and insulin. Evaluation of these hormones will be important to study in the future in order to develop a more complete understanding of the impact of hormonal shifts in pregnancy on breastfeeding success. As well, our measurement of the CAR only included two time points (wake up and 30 minutes after awakening). It is recommended that future studies include additional samples following awakening (45 and 60 minutes after awakening) to provide a more precise assessment of the CAR. Finally, this sample was also selected to be at low risk for adverse maternal and neonatal outcomes. Thus, results may not be representative of the associations among maternal distress, diurnal cortisol, and breastfeeding among higher risk pregnant women.

Conclusions

Results from this study revealed that women who reported lower socioeconomic status in pregnancy were less likely to breastfeed. This association was mediated by cortisol awakening responses over pregnancy. While we are not able to infer causality, findings suggest that dysregulated maternal HPA activity in pregnancy may be related to breastfeeding success in the postpartum period. Therefore, in order to increase the initiation of breastfeeding and positively influence maternal and infant health, it may be important to address factors that impact maternal stress and HPA regulation during pregnancy. More research is needed to replicate these findings in order to better understand the associations

between maternal distress, HPA activity in pregnancy, and breastfeeding behavior in the postpartum period.

Acknowledgments

We would like to thank the women in the study for their participation. Funding for this study was provided by NIMH grant (*omitted for blind review*).

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Figure 1.

Maternal diurnal cortisol patterns in pregnancy differs by breastfeeding status

Salivary cortisol values were log transformed for analyses. Raw values are presented in the figure. Repeated measures analysis indicated that women who reported formula feeding had lower cortisol awakening responses over pregnancy compared to women who breastfed or breast and formula fed. Within each time period, we found that cortisol awakening responses were significantly lower among women who formula fed compared to those who mixed fed at 24 weeks' gestation.

Table 1.

Maternal and infant characteristics by breastfeeding group

	Breastfeeding	Formula Feeding	Breast & Formula	
	<i>N=66</i>	<i>N=36</i>	<i>N=95</i>	
	<u>Maternal Characteristics</u>			
	Mean (SD)/ %	Mean (SD)/ %	Mean (SD)/ %	<i>p</i> -value
Pre-pregnancy BMI	24.57 (5.92)	28.89 (7.95)	25.46 (5.55)	.004
Maternal Age	29.26 (4.8)	23.19 (3.69)	25.98 (5.61)	<.001
Race/ethnicity (% Caucasian)	80%	53%	57%	.01
GDM (% yes)	4%	14%	11%	.24
Hypertension (% yes)	8%	6%	6%	.92
Preeclampsia (% yes)	2%	0%	2%	.68
Parity	1 (1)	1 (1)	1 (1)	.18
Delivery mode (% C-section)	27%	31%	24%	.75
	<u>Infant Characteristics</u>			
	Mean (SD)/ %	Mean (SD)/ %	Mean (SD)/ %	<i>p</i> -value
Gestational age at Birth (weeks)	40 (1)	40 (1)	39 (2)	.67
Small for Gestational Age (% yes)	6%	3%	6%	.73
APGAR Score (5 minutes)	9 (.25)	9 (.58)	9 (.54)	.11

Note. GDM = Gestational Diabetes Mellitus.

Table 2.

The association between socioeconomic status (SES) and breastfeeding is mediated by cortisol awakening response

Variable	β	s.e.	p-value	95% Confidence Interval
Model 1:				
Formula vs. breastfeeding ¹				
SES	-2.03	.67	.002	.04-.49
Mixed vs. breastfeeding				
SES	-1.20	.57	.04	.10-.92
Model 2:				
Formula vs. breastfeeding ²				
SES	-.93	.97	.34	.06-2.66
CAR (24 weeks' gestation)	.19	.96	.84	.18-7.93
CAR (30 weeks' gestation)	.14	1.00	.89	.16-8.22
CAR (36 weeks' gestation)	.16	1.05	.88	.15-9.16
Mixed vs. breastfeeding				
SES	-1.02	.76	.18	.08-1.60
CAR (24 weeks' gestation)	.72	.73	.32	.50-8.61
CAR (30 weeks' gestation)	.65	.72	.36	.47-7.78
CAR (36 weeks' gestation)	.86	.77	.26	.52-10.64

Note. All analyses are adjusted for maternal age, pre-pregnancy BMI, and race. Breastfeeding group has three categories: exclusive breastfeeding, exclusive formula feeding, and mixed feeding. Breastfeeding is the reference category.

¹Log likelihood=260.56, df=8, p<.001.

²Log likelihood=153.08, df=14, p<.001.