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Active Ghrelin and the Postpartum

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Abstract

Purpose—Postpartum depression (PPD) occurs in 10%–15% of women. The appetite hormone ghrelin, which fluctuates during pregnancy, is associated with depression in nonpregnant samples. Here, we examine the association between PPD and active ghrelin from pregnancy to postpartum. We additionally examine whether ghrelin changes from pregnancy to postpartum and differs between breastfeeding and non-breastfeeding women.

Methods—Sixty women participated in a survey examining PPD and had information in regard to ghrelin concentrations were included in the study. The Edinburgh Postnatal Depression Scale was used to assess symptoms of PPD. Raw ghrelin levels and ghrelin levels adjusted for creatinine were included as outcomes.

Results—Women screening positive for PPD at 12-weeks postpartum had higher pregnancy ghrelin concentrations. Ghrelin concentrations significantly decreased from pregnancy to 6-weeks postpartum and this change differed based on pregnancy depression status. Finally, ghrelin levels were lower in women who breastfed compared with women who were bottle-feeding. No significant findings remained once ghrelin levels were adjusted for creatinine.

Conclusions—Although results do not suggest an association between PPD and ghrelin after adjusting for creatinine, future research should continue to explore this possibility extending further across the postpartum period with larger sample sizes.

Keywords

Ghrelin; Postpartum; Depression; Breastfeeding

Major depression is a common psychiatric disorder with a lifetime prevalence of approximately 17% (Kessler et al. 2005; Kessler et al. 1994). Although the etiology of major depression is unclear, biological factors are likely involved. For example, vulnerability to depression increases in females during periods of substantial reproductive hormone change, including puberty (Nolen-Hoeksema and Girgus 1994), perimenopause (Schmidt et al. 2004), and postpartum. After childbirth, approximately 15% of women suffer postpartum depression (PPD; defined as a major depressive episode with onset within the 4-weeks post-delivery) (Gaynes et al. 2005; Pearlstein et al. 2009) and 40% to 80% develop transient,

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Conflict of Interest

None.

milder symptoms (Flores and Hendrick 2002). Women who have experienced a previous major depressive episode are at the greatest risk for developing PPD (Cohen et al. 2006). PPD, in part, is thought to be due to the rapid and substantial gonadal steroid changes that occur during postpartum (Bloch et al. 2003). However, no consistent associations between estradiol and progesterone concentrations and PPD have been identified. Given the significant impact PPD can have on the new mother and her newborn, elucidating the factors involved in vulnerability is essential (Field 2010).

The hormone ghrelin, best known for its roles in meal initiation and nutrient sensing (Cummings et al. 2001; Sun et al. 2008; Wang et al. 2008), also modulates reproduction by regulating hormone secretion from the brain and affecting gonadal tissue development and steroidogenesis (Angelidis et al. 2012). Ghrelin fluctuates over the course of pregnancy and postpartum, peaking in the second trimester, declining steadily thereafter, and reaching its lowest concentration at the end of the third trimester (Fuglsang et al. 2005; Palik et al. 2007). Ghrelin concentrations are lower in pregnant compared with nonpregnant healthy women (Larson-Meyer et al. 2010) and, among postpartum women, vary as a function of lactation. Specifically, significantly lower ghrelin concentrations are observed in non-lactating/bottle-feeding women compared with women who breastfeed for ≥ 6 months (Stuebe et al. 2011) but not compared to those who breastfeed for ~1 month (Larson-Meyer et al. 2010).

There is also mounting evidence that ghrelin plays a regulatory role in mood and sleep (Chuang and Zigman 2010; Lutter et al. 2008; Steiger et al. 2011), both of which often show significant change during pregnancy and postpartum. Exogenous administration of ghrelin is associated with significantly less depression-like symptoms in animal models of depression (Lutter et al. 2008; Steiger et al. 2011). In humans, patients with depression exhibit a significantly lower ghrelin concentration (Barim et al. 2009) and different frequencies of the Leu72Met ghrelin gene variants (Nakashima et al. 2008) than controls. Moreover, there is suggestive evidence that ghrelin administration in humans improves mood in some healthy (Schmid et al. 2005) and depressed (Kluge et al. 2011) individuals.

In addition, ghrelin seems to exert sleep-promoting effects. Ghrelin knockout mice sleep less than wild type mice (Szentirmai et al. 2007); and, in humans, nocturnal ghrelin concentration is blunted during sleep deprivation (Dzaja et al. 2004) but elevated during the day and evening following sleep deprivation (Schmid et al. 2008; Spiegel et al. 2004). Given that ghrelin fluctuates across pregnancy and postpartum and is associated with the changes in mood and sleep often observed during this time, it stands to reason that PPD status may influence ghrelin concentrations.

The purpose of this exploratory study is two-fold. First, we examine preliminary associations between ghrelin concentrations and depressive symptoms from pregnancy to postpartum. Second, we explore ghrelin concentration changes across pregnancy and postpartum and the influence of breastfeeding on ghrelin levels. We do not make *a priori* hypotheses about results or the directionality of the findings as this study is preliminary in nature and initial findings will be important in generating hypotheses about changes in

ghrelin concentration over the course of pregnancy and postpartum and the potential association between ghrelin and PPD.

MATERIALS AND METHODS

Participants

The current sample includes a subsample of 60 women who are part of a larger survey examining PPD in patients from a public health prenatal clinic. Because these secondary analyses were not a planned analysis of the parent study, the selection of this subsample of women was based on the availability of a urine sample. For the overarching survey, eligible patients had to be 18–42 years-old. Medical records were reviewed to identify potential participants attending the public health prenatal clinic, who were then described the study by clinic nurses. Potential participants then provided written informed consent and were screened for participation at 31–33 weeks of pregnancy. Because a previous major depressive episode significantly increases risk for the development of PPD, approximately half of the overarching study sample was selected based on a positive screen for previous depressed mood or anhedonia for at least 2 weeks. For eligible participants, baseline measures were completed during pregnancy at 35–36 weeks and follow-up measurements were repeated at 6- and 12-weeks postpartum.

The following exclusion criteria were included within the larger survey: 1) history of a psychotic/bipolar disorder or substance dependence (or recent use of street drugs or alcohol during pregnancy); 2) eating disorder diagnosis in the past 2 years; 3) body mass index (BMI) > 35 or < 18.5; 4) chronic or acute serious medical illness or pregnancy complications; 5) medications during the two weeks prior to the home visit at 35–36 weeks of pregnancy or during the protocol (except vitamins, iron, acetaminophen, diphenhydramine or for pain control during labor and delivery and short duration treatments for brief, mild illnesses); 6) cigarette smoking; and 7) not fluent in spoken and written English or Spanish.

All assessments were completed during home visits. Questionnaires were administered, and interviews were conducted, in English or Spanish depending on the primary language of the participant. The current subsample consisted of young women (M=26.90; SD=6.0 years) who were over-representative of racial/ethnic minorities in the local community: 17% of women self-identified as Caucasian, 3% Asian, 2% Native American, and 78% “Other;” 87% of the sample self-reported Hispanic ethnicity.

The study was approved by the University of North Carolina Biomedical Institutional Review Board as well as the Wake County Human Services Board and conducted in accordance with The Code of Ethics of the World Medical Association.

Measures

The Edinburgh Postnatal Depression Scale (EPDS) (Cox et al. 1987) was used to assess PPD; it is a widely used measure and has been validated on Spanish-speaking populations (Garcia-Esteve et al. 2003). Compared to other depression measures, the EPDS relies less heavily on questions about somatic or physical symptoms of depression and includes several

items that specifically assess for symptoms of anxiety. A cut-off score of 12 or higher has consistently shown to correlate with a diagnosis of major depressive disorder (Cox et al. 1987; Matthey et al. 2006; Murray and Carothers 1990). At 6- and 12-week follow-up visits, participants were asked how frequently they were: 1) bottle-feeding, 2) breastfeeding, or 3) breastfeeding and bottle-feeding.

Ghrelin Samples

sTwenty-four hour urinary samples were collected during pregnancy (baseline) and again at 6-weeks postpartum. Only 24-hour urine collections ≥ 900 mL were considered valid. Samples were frozen at −80°C until assayed in batch. The 24-hour urine was carefully processed to maintain hormone integrity (i.e., prevent deactylation) by keeping it cold and acidic. Active ghrelin levels were measured using a commercially available competitive double antibody radioimmunoassay reagents and protocol (Millipore Corp, Billerica, MA). This assay has a standard curve ranging from 7.8 to 1000 pg/mL; the sensitivity of the assay is 7.8 pg/mL. The antibody cross-reacts 100% with the bioactive form of ghrelin with octanoyl group on serine 3, and with ghrelin 1–10; it reacts < 0.1% with des-octanoyl ghrelin, ghrelin 14–28, leptin, insulin, glucagon, and glucagon-like peptide 1 7–36. This assay has been shown to yield active ghrelin levels in urine comparable to those measured by high performance liquid chromatography (Aydin et al. 2008). However, because this assay was not designed for urine, we performed a dilution study and determined that a 1:1 to 1:3 dilution in the assay buffer gave good reproducibility. Thus, a 1:1 dilution in assay buffer was used for this study. To examine the potential impact of fluid shifts during pregnancy, we examined both raw ghrelin levels and creatinine-adjusted levels as outcomes.

Statistical Analysis

We confirmed the normal distribution of our primary measures, EPDS and ghrelin, at pregnancy (i.e., skewness = 0.6 and −0.1, respectively) and, therefore, did not transform any variables prior to analysis. Because we consider our study exploratory, we chose *a priori* not to include any covariates in the models.

We created two dichotomous PPD variables. First, PPD status, based on the EPDS cut-off score such that those women scoring at or above the cut-off of 12 were coded as a positive screen for depression (‘1’) and those scoring below 12 were coded as a negative screen for depression (‘0’) during pregnancy and 6- and 12-weeks postpartum. Second, we created a variable, based on PPD status, to determine how many women reported change in depression status over the course of pregnancy and postpartum, “PPD-change:” 1) no depression at pregnancy or postpartum; 2) no depression at pregnancy, but PPD at 6- or 12-weeks postpartum; 3) depression at pregnancy and PPD at 6- or 12-weeks postpartum; 4) depression at pregnancy, but no PPD at 6- or 12-weeks postpartum. Because so few women reported breastfeeding only at 6- or 12-week follow-up (n=8 and 7, respectively), and because we found no differences in ghrelin as a function of the three feeding methods (1=bottle-feeding, 2=breastfeeding, 3=bottle- and breastfeeding), we collapsed groups 2 and 3 to create two categories: bottle-feeding only and some combination of breastfeeding and bottle-feeding.

We examined group differences, based on PPD status and PPD-change, in mean ghrelin concentrations using a mixed between-within subjects repeated measures analysis of variance and we examined the association between EPDS total score and ghrelin using linear regression. Next, we explored the change in ghrelin concentration from pregnancy to 6-weeks postpartum using a paired samples t-test. Finally, an analysis of variance was used to examine mean differences in active ghrelin between women who strictly bottle-fed compared with women who breastfed or combined breastfeeding with bottle-feeding. All analyses were completed with both raw ghrelin levels and creatinine-adjusted ghrelin levels to understand our results within the context of the fluid shifts that occur in pregnancy and postpartum. Significance tests were two-tailed and significance was assessed at $p < 0.05$.

RESULTS

The mean EPDS score during pregnancy was 6.42 (SD=4.24) and at 6- and 12-weeks postpartum was 5.20 (SD=4.40) and 4.42 (SD=4.14), respectively. The percentage of women reporting an EPDS score at or greater than 12 (suggesting major depression) was 13.33% (n = 8) at baseline, 11.67% (n = 7) at 6-weeks postpartum, and 6.67% (n = 4) at 12-weeks postpartum. Three women reported pregnancy depression and remained depressed at 6- and/or 12-weeks postpartum, five reported pregnancy depression and no postpartum depression, and five reported no pregnancy depression but were depressed at 6- or 12-weeks postpartum.

Mean raw and creatinine-adjusted ghrelin concentrations based on PPD status and PPD-change are shown in Tables 1 and 2, respectively. A significant mean difference in raw ghrelin concentration was observed at 12-weeks postpartum such that women screening positive for PPD at 12-weeks postpartum had higher mean active ghrelin concentration during pregnancy compared with women who did not screen positive for PPD at 12-weeks postpartum, $F(1, 47)=5.12$, $p < .05$. A trend ($p = 0.05$) was also observed for raw ghrelin levels at 6-weeks, with women screening positive for PPD having higher 6-week ghrelin concentrations than those not screening positive for PPD. Similarly, a significant interaction was observed between pregnancy PPD status and time, $F(2, 47)=15.60$, $p < .01$, suggesting that change in ghrelin levels from pregnancy to postpartum differ based on pregnancy depression status. Specifically, ghrelin concentrations decreased less in women who were depressed during pregnancy (M= −36.41; SD=21.40 pg/mL) compared with women who were not depressed during pregnancy (M= −47.30; SD=40 pg/mL). No significant associations emerged with raw ghrelin levels and PPD-change. When analyses were repeated with creatinine-adjusted ghrelin concentrations, no findings remained significant. Further, we observed no significant associations between pregnancy, 6-week postpartum, or 12-week postpartum EPDS total scores and raw or creatinine-adjusted ghrelin concentrations.

Finally, raw mean ghrelin concentrations significantly decreased from pregnancy (M=132.20, SD=28.37 pg/mL) to 6-weeks postpartum (M=88.47, SD=32.00 pg/mL), $t(48)=8.83$, $p < .001$. Results were similar for creatinine-adjusted ghrelin, which significantly decreased from pregnancy (M=128.00, SD=46.24 pg/mL) to 6-weeks postpartum (M=83.23, SD=29.00 pg/mL), $t(49)=6.00$, $p < .0001$. We also observed a significant mean difference in raw ghrelin levels at 6-weeks postpartum based on

breastfeeding status at 6-weeks postpartum, $F(1, 47)=5.23$, $p < .05$. Active ghrelin concentrations were lower in women who reported breastfeeding (M=84.40; SD=30.62 pg/mL) compared with women who were bottle-feeding only (M=113.0; SD=31.00 pg/mL). However, no mean differences in creatinine-adjusted ghrelin concentrations based on breast-feeding status were observed.

DISCUSSION

This study is the first, to our knowledge, to explore the relation between PPD and active ghrelin concentrations and adds to a small but growing literature describing longitudinal changes in active ghrelin from pregnancy to postpartum. We observed a higher pregnancy active ghrelin concentration among the subset of women who screened positive for PPD at 12-weeks postpartum compared with those who screened negative for PPD. Thus, because raw ghrelin concentrations decrease from pregnancy to postpartum, women who have high active ghrelin levels during pregnancy and subsequently experience a decrease in ghrelin at postpartum may be especially vulnerable to depressive symptoms given the significant association between low ghrelin levels and depression in nonpregnant samples (Barim et al. 2009).

It was also observed that raw ghrelin concentrations change from pregnancy to postpartum differently in women who were depressed during pregnancy compared with those women who were not depressed at pregnancy. Examining mean change scores in ghrelin levels from pregnancy to postpartum indicated that women who were depressed during pregnancy experienced less change in ghrelin levels between pregnancy to postpartum. Importantly however, when ghrelin levels were adjusted for creatinine our findings were no longer significant. Given that creatinine can be considered a marker of renal function and fluid retention, this suggests that the fluid shifts that occur during pregnancy and postpartum are an important factor in ghrelin levels and may entirely account for the association between ghrelin and depression during the pregnancy and postpartum period.

Our findings suggest that active ghrelin (both raw and creatinine-adjusted levels) decreases from pregnancy to 6-weeks postpartum; as such, they are contrary to previous observations suggesting an increase in active ghrelin from pregnancy to 24 hours postpartum (Baykus et al. 2012), but consistent with those indicating decreased active ghrelin at 30 to 180 days postpartum (Ilcol and Hizli 2007). This time course (i.e., an initial spike in active ghrelin levels postpartum followed by a continual decrease over time) makes physiological sense from the perspective of ghrelin facilitating adequate food intake to meet the energy demands of mother and infant and to support milk production during a critical window for establishing breastfeeding and later returning food intake and weight to homeostasis over time.

Consistent with previous research we observed that women who were breastfeeding at 6-weeks postpartum had lower raw active ghrelin concentrations than women who were bottle-feeding only. This finding does corroborate a previous report showing that active ghrelin concentrations steadily decreased in breastfeeding women over a period of 180 days (Ilcol and Hizli 2007). Similarly, lactating women (Aydin et al. 2006; Ilcol and Hizli 2007; Larson-

Meyer et al. 2010) and animals (Shibata et al. 2004) have decreased ghrelin concentrations. Active ghrelin concentrations may decrease in breastfeeding women secondary to diminished estradiol concentrations in women (McNeilly et al. 1994), as estradiol may play a role in ghrelin production (Kellokoski et al. 2005; Sakata et al. 2006). In turn, diminished circulating active ghrelin may play a role in postpartum weight loss in breastfeeding women, who tend to retain less pregnancy weight compared to non-breastfeeding women (Baker et al. 2008; Olson et al. 2003). However, we did not observe significant differences in ghrelin concentrations based on breastfeeding status in creatinine-adjusted ghrelin levels again suggesting the potential importance of pregnancy and postpartum renal function on ghrelin levels.

Several limitations of this study should be noted. First, and foremost is our sample size. Because of our small sample size of women with PPD, results should be interpreted with caution. Second, it is also possible that our preliminary study was underpowered to detect significant effects. Third, the larger parent study was an enriched sample of women with depression during pregnancy. Thus, findings may not generalize to epidemiological samples. Fourth, not assessing active ghrelin beyond postpartum week six prevented us from exploring potentially interesting questions about associations between ghrelin and depression further into the postpartum period. Fifth, we only assayed active ghrelin concentrations and did not have information on total ghrelin (sum levels of both the active and inactive forms) concentrations. Since active and total ghrelin are differentially regulated in breastfeeding women and are differentially associated with ghrelin levels in breast milk (Ilcol and Hizli 2007), future studies examining both active and total ghrelin in women with PPD who do and do not breastfeed would be worthwhile. Further, due to the limited number of women reporting breastfeeding only, we had to combine those women who were breastfeeding only and those who were engaging in a combination of breastfeeding and bottle-feeding. We may have found results in line with previous studies if our sample size of breastfeeding only women was larger. Finally, although the cut-off used for the EPDS score in this report is a well-established cut-off suggestive of PPD, the use of cut-offs could have impacted findings such that we may have observed differing findings with a different cut-off (e.g., score of 11 or 13 versus 12).

Taken together, our results, in general, suggest that once renal function is accounted for, there is no significant association between ghrelin concentration and PPD. It will be important for future research to consider renal function and creatinine levels when assessing the association between ghrelin and depression. Because PPD can have serious consequences for mother and infant, it is imperative that we improve our knowledge of the biological factors associated with PPD. Future studies that extend further across the postpartum period, assess total and active ghrelin concentrations, evaluate depression by diagnostic interview rather than self-report, and include larger cohorts of breastfeeding and bottle-feeding mothers in epidemiological samples are needed before we will be able to draw definitive conclusions about the association between PPD and ghrelin.

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Table 1

Mean (SD) Active Ghrelin Concentrations (pg/mL) by PPD Status

	Pregnancy PPD		6-week Postpartum PPD		12-week Postpartum PPD	
	Positive	Negative	Positive	Negative	Positive	Negative
Pregnancy Ghrelin	145.49 (25.70)	130.14 (28.60)	150.00 (28.00)	130.00 (27.86)	162.17 (15.54)	130.05 (28.00)
6-weeks Postpartum Ghrelin	108.96 (28.00)	84.47 (31.50)	102.12 (32.60)	86.20 (32.00)	118.90 (34.00)	85.80 (30.80)
Pregnancy Creatinine Adjusted Ghrelin	126.30 (7.00)	128.00 (50.00)	132.70 (28.10)	127.10 (48.30)	125.00 (5.64)	128.00 (48.00)
6-weeks Postpartum Creatinine Adjusted Ghrelin	90.80 (19.30)	81.80 (30.00)	86.00 (23.00)	83.00 (30.00)	96.42 (32.00)	82.10 (28.34)

Note. PPD=Postpartum Depression.

Table 2

Mean (SD) Scores for Active Ghrelin Concentrations (pg/mL) Across Pregnancy and Postpartum By PPD Change Status

	No Depression (n=47)	Pregnancy Depression/PPD (n=3)	Pregnancy Depression/No PPD (n=5)	No Pregnancy Depression/PPD (n=5)
Pregnancy Ghrelin	129.22 (28.71)	164. 36 (12.53)	134.20 (23.70)	139.00 (28.6)
6-weeks Postpartum Ghrelin	84.10 (33.03)	133.20 (25.10)	94.42 (23.70)	87.23 (19.04)
Pregnancy Creatinine Adjusted Ghrelin	127.17 (51.30)	127.30 (5.00)	125.66 (8.24)	135.43 (34.00)
6-weeks Postpartum Creatinine Adjusted Ghrelin	81.20 (31.04)	97.50 (30.00)	86.71 (12.35)	85.82 (23.21)

Note. PPD=Postpartum Depression.