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Exploring dissociation and oxytocin as pathways between trauma exposure and trauma-related hyperemesis gravidarum: a test-of-concept pilot

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Abstract

Posttraumatic stress disorder (PTSD) is associated with gastrointestinal and genitourinary comorbidities. These map onto the somatization disorder symptoms in the Diagnostic and Statistical Manual of Mental Disorders (APA, 1994) and the dissociative [conversion] disorders symptoms in the International Classification of Diseases taxonomy (WHO, 2007). Hyperemesis gravidarum (HG) is one of these symptoms and a gastrointestinal comorbidity of PTSD occurring in pregnancy. It is an idiopathic condition defined as severe vomiting with dehydration, metabolic imbalance, wasting, and hospital care-seeking. HG is more severe than the normative phenomenon of nausea and vomiting of pregnancy (NV). This test-of-concept pilot (N=25) explored the hypothesis that there is a trauma-related subtype of HG characterized by (1) high levels of dissociative symptoms and (2) altered plasma concentrations of oxytocin. This hypothesis is informed by a theory of posttraumatic oxytocin dysregulation positing altered oxytocin function as a mechanism of gut smooth muscle peristalsis dysfunction. A four-group analysis compared controls with nausea and vomiting of pregnancy (NV only) and cases with HG only, NV and PTSD, or HG and PTSD. Oxytocin was correlated with nausea and vomiting symptom severity

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score ($r = .464$, $p = .019$) and with the dissociation symptom score ($r = .570$, $p = .003$). Women in the group with both PTSD and HG (the “trauma-related HG subtype”) had the highest levels of dissociation and the highest levels of oxytocin. A linear regression model indicated that the independent association of the trauma-related HG subtype with oxytocin level was mediated by high levels of dissociative symptoms.

Keywords

Oxytocin; Dissociative disorder; hyperemesis gravidarum; posttraumatic stress

Childhood maltreatment and posttraumatic stress sequelae, including the associated feature of dissociation, have been associated with physical morbidity among women, including comorbid functional and pain conditions affecting genitourinary and gastrointestinal smooth muscle (Seng, Clark, McCarthy, & Ronis, 2006). We refer to these gastrointestinal and genitourinary conditions, irritable bowel syndrome, chronic pelvic pain, dysmenorrhea, dyspareunia, and painful bladder syndrome, collectively as “pelvic visceral dysregulation” (PVD) disorders and theorize that dysregulated oxytocin function might be a common plausible biological mechanism (Seng, 2010). This “posttraumatic oxytocin dysregulation disorder” theory specifies these propositions: (1) Dissociation could be a psychological pathway between early relational trauma and disorders of smooth muscle regulation in the organs of the pelvis and gut. (2) Oxytocin could be a physiological mechanism. (3) And dissociation and oxytocin could be interacting. A dose-response association of PTSD and dissociation with these PVD disorders has been documented in service use data (Seng, Clark, McCarthy, & Ronis, 2006). For reasons explained below, we consider the severe vomiting of pregnancy, hyperemesis gravidarum (HG), also to be a PVD disorder which is occurring in the context of pregnancy.

Background on oxytocin

Oxytocin, a small peptide, is a neurotransmitter and a hormone secreted centrally from the posterior pituitary, as well as a paracrine hormone secreted peripherally from tissues such as the gut, bladder, uterus in females, and vas deferens in males. Human studies demonstrate numerous roles for oxytocin in physical aspects of daily life of males and females across the lifespan including growth, wound healing, fluid balance, blood pressure and breathing regulation via control of vascular and bronchial dilatation, and digestion and sexual and reproductive functions including birth and breastfeeding via control of smooth muscle peristalsis (Pederson, Caldwell, Jirikowski, & Insel, 1992; Uvnas Moberg, 2003). Oxytocin is active in regulating vagal tone (Porges, 2011), and could be associated with dysregulation of any tissues and organs regulated by the vagus nerve.

Oxytocin is implicated in behavioral aspects of daily life in relation to attachment, affiliation, and maternal behavior (Pederson, Caldwell, Jirikowski, & Insel, 1992), pro-social behavior (Brown & Brown, 2006), stress regulation (Porges, 2011), and memory and learning under very stressful conditions (Pitman, Orr, & Lasko, 1993), especially social learning (Hurlemann et al., 2010). In literature focusing on biobehavioral outcomes of maternal-infant dyadic regulation, dysregulation of the oxytocin system has been considered a potential mechanism of adverse outcomes of early relational trauma such as attachment disorganization and affect dysregulations associated with self disorders (i.e., dissociation, somatization, interpersonal sensitivity) (Schoore, 2003). This is consistent with the cascade model of the effects of deleterious early experience on neurobiology (Teicher, Anderson, Polcari, Anderson, & Navalta, 2002) which specifies the oxytocin system as a third “pillar”

of the stress-response system, along with the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system.

The posttraumatic oxytocin dysregulation theory (Seng, 2010) posits that self disorders and pelvic visceral disorders could be maintained or exacerbated by subsequent abuse trauma and by chronic posttraumatic reactions which are associated with dysregulation in other stress-responses (i.e., HPA, gaba-glutamate, dopamine, and serotonin systems). This could occur because the HPA axis and oxytocin system are mutually regulating or because oxytocin is an intermediary between stress response and the release of other hormones (Liberzon & Young, 1997; Uvnas-Moberg, 2003).

Background on hyperemesis gravidarum

A 2001 study of PTSD and physical complications of pregnancy (Seng et al., 2001) found an 8% rate of HG among Medicaid recipients with PTSD diagnosis, an odds ratio of 3.9. Nausea and vomiting of pregnancy (NV) affects 70% of women to some extent during early pregnancy and is considered a normal aspect of healthy pregnancy. HG is a severe, unremitting form of nausea and vomiting defined by its impact on hydration, metabolic status, wasting, and treatment-seeking at a hospital (Buckwalter & Simpson 2002). Although HG occurs in only 0.5% to 3% of pregnancies, it is the second leading cause of hospitalization of pregnant women, accounting for 9.3% of U.S. pregnancy admissions and resulting in considerable health care expenditure as well as disability (Gazmararian et al., 2002). Current treatments aim to control the nausea and vomiting symptoms and maintain metabolic status.

In literature over the past century, authors have speculated that HG has a psychogenic cause or is a “hysterical” condition, connoting an underlying sexual trauma. Recently favored is the converse theory, that HG is so distressing that it causes psychological morbidity (Buckwalter & Simpson, 2002). Other theorized etiologies range from sensitivity to pregnancy hormones, to osmotic pressure changes affecting the middle ear, to increased reactivity to minor food toxicity. We advanced a middle ground point of view whereby vomiting, which is a non-specific sign, could indicate any of several etiologies—singly or in combination—for any woman, positing that there logically could be subtypes of HG. We tested the hypothesis that there is a psychogenic subtype in an epidemiologic analysis of health insurance claims data (Seng, Schrot, van de Ven, & Liberzon, 2007). One in five women with HG had either a pre-pregnancy psychiatric diagnosis or a co-occurring diagnosis for functional somatic disorders, or both. Increased risk for HG with both diagnoses suggested that a minority of HG cases could have a psychogenic etiology. We referred to this hypothesized subtype as “posttraumatic HG.”

Purpose of this study

This test-of-concept pilot initially hypothesized that HG would be associated with PTSD, and that oxytocin dysregulation would be a plausible biological mechanism. Subsequently, when PTSD-affected women were encountered in equal numbers in the HG case group and NV control group, we extended the hypothesis to consider that it may be dissociation rather than PTSD *per se* that is associated with HG. The recently explicated posttraumatic oxytocin dysregulation theory (Seng, 2010) arose partly as a means to make sense of this pilot’s findings as well as findings from our previous studies, and from literature on PTSD and physical comorbidities. The psychological symptoms of PTSD and dissociation could be the manifestations that clinicians have observed over the past century in some HG cases, accounting for the psychogenic etiology hypothesis.

Methods

Design

This paper reports a test-of-concept case control pilot study with the hypothesis that there is a trauma-related subtype of HG characterized by (1) high levels of dissociative symptoms and (2) significantly different plasma concentrations of oxytocin. Participants were selected for having nausea and vomiting, either typical nausea and vomiting of pregnancy (controls) or meeting the definition of HG (cases). PTSD status was determined during the protocol. When equal numbers of women with PTSD were found in the HG and NV groups, we moved from a two-group to a four-cell design for analysis, classifying women as having (1) NV only, (2) HG only, (3) NV and PTSD, or (4) HG and PTSD.

Sample and recruitment

Women were recruited as HG cases if they met HG diagnostic criteria: dehydration, metabolic disturbance, and hospital treatment-seeking. They were recruited during their first emergency department visit, early in the course of the disorder, to minimize risk that any psychiatric disorder measured during the protocol would be attributable to the HG. NV controls were recruited via community fliers. We used the Pregnancy Unique Quantification of Emesis (PUQE) instrument (Koren et al., 2002) which rates each element (nausea, vomiting, dry heaves) on a 1 to 5 scale. The controls were recruited to fill three levels of stratification based symptom severity: asymptomatic (PUQE score 3–5), mild NV (score 6–9), and moderate NV (score 10–12). PUQE score at the time of recruitment was assessed, but it was not a selection criterion. Volunteers were excluded if they were smoking, non-English speaking, greater than 16 weeks gestation, with history of psychotic illness, sick with other acute illness, or diagnosed with molar pregnancy or multiple gestation since these are associated with elevated oxytocin levels. Women were not required to stop use of any antiemetic they were taking. This protocol was approved by the Institutional Review Board of our university and all participants gave written informed consent.

Procedures

Data collection took place in the General Clinical Research Center at our hospital. Originally the protocol lasted 24 hours, involving an inpatient stay and sampling blood for oxytocin every four hours in the “diurnal protocol.” After analysis of 16 participants’ data, which showed no diurnal pattern for oxytocin, we revised the protocol to an 8-hour daytime stay. In the revised protocol, we focused on detecting pulsatility using Nyquist’s Sampling Theorem (Nyquist, 1928) by drawing blood samples for oxytocin every 10 minutes across an 80-minute period between 10:30 am and noon in the “pulsatility protocol.”

The protocol began with assessment of urine specific gravity, placement of the indwelling intravenous catheter, and administration of intravenous fluid as needed to achieve a specific gravity of less than 1.030. A 30-minute post-venipuncture stress-recovery period passed prior to sampling of oxytocin. Initial samples were drawn for pregnancy hormones that might be confounds or alternative explanations for HG, including estradiol, progesterone, and human chorionic gonadotropin. Specimens transferred to iced anti-coagulant-treated tubes containing a protease inhibitor, centrifuged (15,000 *g* for 15 minutes at 5°C), pipetted into 2 mL polypropylene aliquots, and stored at –80°C until assay.

The psychiatric diagnostic interview took place beginning at 2:00 pm so as not to affect any oxytocin sample if the trauma history was stressful. The Life Stressor Checklist (Wolfe & Kimerling, 1997) assesses lifetime exposure to 30 potentially traumatic events. We created three trauma history variables: childhood abuse, adult abuse, and sum of lifetime trauma exposures. The National Women’s Study PTSD Module (Kilpatrick et al., 1994), yields a

symptom count variable (0–17) and a current PTSD case variable based on the DSM-IV symptom clusters criteria. Dissociative symptoms were measured with the 8-item taxomic version of the Dissociative Experiences Scale (DES-T) (Waller, Carlson & Putnam, 1996), modified to permit verbal responses on a 1–5 scale, occurring never, rarely, sometimes, often, or all the time. We used a median split as a lower- versus higher-dissociation grouping variable.

Enzyme immunoassay of oxytocin was done using a commercially available kit. The inter- and intra-assay coefficients of variance were 12.3% and 8.6%. The assay is reported to be highly sensitive (minimal detection rate = 4.68 pg/mL) with very little antibody cross-reactivity for other neuropeptides (Assay Designs, Inc., 2001).

Analyses

We conducted preliminary analyses of the interview and assay data to assess for missing data, relationships among variables, and normality in error variance and to verify that it was not problematic to combine the data from the two protocols. These two samples did not differ on any background characteristic or independent variable. Both protocols had noon oxytocin samples, for which the means and standard deviations did not differ. Therefore hypothesis testing and modeling were conducted with the noon samples from both protocols. Oxytocin values are presented in pg/mL, the natural log was used for hypothesis testing and modeling.

We compared the four groups on demographic, pregnancy, trauma history, mental health, nausea and vomiting. We conducted ANOVAs as bivariate tests of the hypotheses that the HG and PTSD group would have the highest level of dissociative symptoms and a significantly different level of oxytocin. We extended the hypothesis test to determine whether dissociation mediates the association between being in the HG and PTSD group and oxytocin level. Given the small sample size and pilot purpose, we accepted 0.1 as the limit of significance for interpretation. SPSS v.17 was used for all analyses.

Results

A total of 27 women were enrolled, 12 HG cases and 15 NV controls. Venous access could not be maintained for two women, one in each group, and they were dismissed from the protocol. Face validity of the case-control assignment was verified by their PUQE score (possible range 3–15) on the day of recruitment. The HG cases had scores from 8 to 15 ($M = 11.4$, $SD = 2.4$). The NV controls had scores from 3 to 10 ($M = 5.9$, $SD = 2.5$; $t(23) = -5.6$, $p < .001$). Ten women met PTSD diagnostic criteria. Half were HG cases, half were NV controls. The following two-by-two cells were formed: NV only ($n = 9$), HG only ($n = 6$), NV and PTSD ($n = 5$), HG and PTSD ($n = 5$).

Characteristics of the sample overall and the four groups are presented in Table 1. The sample was demographically diverse. Half were expecting their first infant. Their mean gestational age was 12 weeks. Seven women were using antiemetic medication, five in the HG only group and two in the HG and PTSD group ($\chi^2 = 14.9$, $p = .002$). The two PTSD groups had more exposure to childhood abuse ($\chi^2 = 8.7$, $p = .034$) and adult abuse ($\chi^2 = 11.9$, $p = .008$), but the sum of lifetime exposures did not differ significantly across groups. The PTSD symptom count rose from a low of 1.8 in the NV only group, 3.3 in the HG only group, 8.2 in the NV and PTSD group, and 12.0 in the HG and PTSD group ($F(3, 21) = 19.8$, $p < .001$), with post hoc Scheffe indicating significant contrasts between both PTSD-affected groups and the PTSD-negative groups (p values ranging from $.045$ to $< .001$). Dissociation symptoms ($M = 10.0$, $SD = 2.9$) were more closely associated with HG status than with PTSD status ($F(3, 21) = 2.6$, $p = .079$), but the difference did not reach statistical

significance. The HG-only group had the highest mean levels of all three pregnancy hormones, though only the human chorionic gonadotropin level difference reached statistical significance ($F(3, 21) = 4.2, p = .019$), with post hoc Scheffe indicating a significant difference in the NV and PTSD group versus HG only group contrast ($p = .032$).

We examined a correlation matrix with all background characteristics, pregnancy hormones, and PUQE, PTSD, and dissociation scores in relation to oxytocin concentration. Only the nausea and vomiting score ($r = .464, p = .019$) and dissociation score ($r = .570, p = .003$) were correlated with oxytocin. The nausea and vomiting and dissociation scores also were correlated with each other ($r = .521, p = .008$).

We compared the four groups on PUQE scores, dissociation scores, and noon oxytocin levels (Table 2). There was no difference in PUQE scores between the HG only and HG and PTSD groups. However, dissociation scores and oxytocin levels were significantly higher in the HG and PTSD group than in the HG only group. Therefore, we additionally tested the hypothesis that it is dissociation, rather than PTSD that is associated with oxytocin levels. We created a *new* four-group variable representing psychiatric subtypes from the two-by-two cross tabulation of PTSD diagnosis and dissociation median split, resulting in the categorical variable: neither PTSD nor dissociation ($n = 10$), PTSD only ($n = 6$), dissociation only ($n = 5$), both PTSD and dissociation ($n = 4$). The cases with both PTSD and dissociation had significantly higher oxytocin, a difference that had a large effect size ($\eta^2 = .610$).

To test the hypothesis that the HG and PTSD group is distinct in its association with oxytocin, we entered into a linear regression model the three dummy group variables, using the NV only control group as the reference category. This hypothesis was affirmed; only the HG and PTSD group was associated with the noon, log-transformed oxytocin level ($\beta = .558, p = .014$, adjusted $R^2 = .172$).

To test the hypothesis that dissociation would mediate the association of trauma-related HG with oxytocin level, we used a linear regression. We used only the trauma-related HG dummy variable in the first step, which was significant ($\beta = .486, p = .014$, adjusted $R^2 = .203$). When we entered the dissociation score in a second step, the trauma-related HG subtype was no longer independently predictive ($\beta = .282, p = .148$), but the dissociation score was predictive ($\beta = .439, p = .029$), and this second model's explained variance increased to 33% by adjusted R^2 . Thus, in this small pilot sample, the hypothesis that dissociation mediates the association of a trauma-related HG subtype with oxytocin level was supported.

To estimate effect size and observed power, we used a general linear model with the four-group variable and the dissociation median split variable as fixed factor main effects. We also specified an interaction due to the mediating effect of the dissociation level. Table 4 and Figure 1 depict this model. The overall model is statistically significant ($p = .005$) with 66% of variance explained and with an observed power of 95.1%. Each of the three predictor variables is associated with oxytocin, at observed power levels that are nearly adequate despite the small sample size (76% for the dissociation median-split factor, 77% for the HG grouping factor, and 81% for the interaction term).

Discussion

This test-of-concept pilot study finds support for the hypothesis that there is a trauma-related subtype of HG and that it is likely characterized by (1) high levels of dissociative symptoms and (2) elevated plasma concentrations of oxytocin. PTSD itself is not associated with elevated oxytocin, nor is HG that occurs in the absence of PTSD. It is women with

comorbidity of PTSD and HG who had higher oxytocin. This finding provides initial evidence for a trauma-related subtype of HG and suggests that dysregulation of the oxytocin system is a plausible biological mechanism warranting further investigation. Symptoms of pathological dissociation mediated the relationship of trauma-related HG with oxytocin. Pathological dissociation occurred in this sample both in combination with PTSD and alone. It was most strongly associated with elevated oxytocin when it was comorbid with PTSD (Table 2). We can tentatively say that dissociation may be a psychological pathway for vomiting in a trauma-related *subtype* of HG. We can also nuance the concept of a “psychogenic” etiology for this subtype of HG to include a plausible biological mechanism in the form of oxytocin dysregulation. These findings suggest that subtype-specific hyperemesis research is warranted to advance tailored treatments that target dissociation and regulate oxytocin.

Strengths and Limitations of the pilot

There numerous strengths to this study. Our sample was diverse and intensively characterized in terms of demographics, psychiatric status, and pregnancy physiology. The protocols were implemented within the highly structured environment of an inpatient research unit. The levels of oxytocin found in this study are consistent with those found in other studies of adult females, including women on hormone replacement therapy (Taylor et al., 2006). The very high levels found in the women with dissociative symptomatology are consistent with higher levels or dysregulation of oxytocin reported in association with mental health conditions, including depression (e.g., Cyranowski et al., 2008).

Consistent with pilot work, the sample size is small. Hence, while the results are intriguing, it is essential that the models be tested on larger samples. In addition to the small sample size, there are several limitations. Oxytocin likely is present in plasma both as a pituitary hormone where it has a stress-response function and as a paracrine hormone where it functions to control smooth muscle contractility. This study measures only plasma (free) oxytocin, shedding no light on density or affinity of receptors in the gut or on the workings of the central nervous system side of the blood-brain barrier. We used a median split to classify the level of dissociation, thus our findings should not be generalized to the diagnostic categories, but rather to those with symptoms of dissociation. We only measured psychological dissociation. Future studies could measure somatoform dissociation as well (Nijenhuis et al., 2003). We did not include depression in this analysis, but it is frequently comorbid with PTSD and should be considered in larger studies. We used only one time point of oxytocin data that was common to both protocols, repeated measures may be useful in future studies. Pulsatility has varied by depression status (Cyranowski et al., 2008), so the use of the frequent sampling protocol, which better captures pulsatility, would be advisable for studies that include depression as a covariate. Another limitation is that we could not directly address the alternative hypothesis that vomiting in HG becomes conditioned, is distressing, and so *causes* psychological morbidity rather than being *caused by* psychological morbidity (Buckwalter & Simpson, 2002). We attempted to minimize this potential confound by recruiting HG cases during their first care-seeking episode. We hope that presentation of these findings supports the notion of a trauma-related psychogenic cause for *some* women without diminishing appreciation that HG is debilitating, distressing, and could feasibly cause PTSD if the course of vomiting becomes life threatening. Finally, although none of the pregnancy hormones were associated with oxytocin, both human chorionic gonadotropin and estradiol were significantly higher among HG cases that did not have PTSD and these hormones should be factored into future studies.

Issues warranting consideration in future research

Two other studies are potentially relevant to this pilot, although their source and samples differed. The connection between altered oxytocin function and specific childhood trauma has been recently supported in a study that found lower levels of oxytocin in cerebrospinal fluid in 14 women selected for a childhood abuse history compared with 8 women with no childhood maltreatment (Heim et al., 2009). The connection between oxytocin and “stomach ache,” potentially a PVD disorder manifesting in young children, has been supported by a study where plasma oxytocin levels were lower in the presence of gastrointestinal pain (Alfven, 2004). These findings of lower oxytocin inside the blood-brain barrier of women child abuse survivors and in plasma of children with stomach pain are potentially at odds with our finding of higher oxytocin levels in the plasma of women with the dissociative sequela of maltreatment experiencing severe vomiting.

To our knowledge, this study’s results are the first to suggest that this pattern of PTSD and dissociation comorbidity (or dissociative subtype of PTSD) may have a biological basis in the oxytocin system. Predominance of anxious versus dissociative posttraumatic stress reactions may be very important in relation to oxytocin. Our pilot results suggest that some women with PTSD have low oxytocin and others have high oxytocin and that this heterogeneity may be explained by dissociation. This dimorphic pattern may be due to a third, unmeasured factor. For example, there is one study (Maes et al., 1999) reporting that people with PTSD have higher levels of prolyl endopeptidase (PEP), an enzyme that lyses peptides.

There was no directional hypothesis in our theory linking oxytocin with PVD disorders in relation to what is happening in the gastrointestinal smooth muscle itself. The impact of high and low plasma oxytocin, or of the density of receptors, awaits a different type of study. Electrogastrography (EGG), which measures gastric electrical activity and peristalsis, has found both hyper- and hypo-activity in studies of hyperemesis (Walsh, Hasler, Nugent & Owyang, 1996). Thus, we recommend that future studies include measures of peristalsis in the target tissues, such as EGG or ultrasound, or other vagal tone indicators, such as heart rate variability to better elucidate the psychophysiological complexity.

The preliminary nature of work on this topic

Research and theorizing about oxytocin and traumatic stress is just beginning (Olf et al., 2010). This research will be complex and will need to consider the factors known to be important in the field of traumatic stress studies, such as age, dose and type of exposure, gender, and patterns of primary diagnosis, comorbidity, and associated features. It will also need to account for oxytocin’s effect on the target tissue and for complexities of the oxytocin system: effects of sex hormones, central versus peripheral measurement, afferent versus efferent signaling, receptor density and affinity, and challenges of measurement related to the small peptide’s short half-life and pulsatility.

The finding from this pilot that PTSD with dissociation, and not PTSD diagnosis by itself, was significantly associated with oxytocin indicates that future studies of trauma-related PVD disorders and oxytocin must better elucidate the full spectrum of trauma-related disorders. Although introducing oxytocin as a biomarker into psychobiological studies of posttraumatic spectrum disorders will increase complexity, it has the potential to increase coherence in our understanding of the impact of trauma on the body.

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References

- Alfven G. Plasma oxytocin in children with recurrent abdominal pain. *Journal of Pediatric Gastroenterology & Nutrition*. 2004; 38:513–517. [PubMed: 15097440]
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition. Washington, DC: Author; 1994.
- Brown SL, Brown RM. Selective investment theory: Recasting the functional significance of close relationships. *Psychological Inquiry*. 2006; 17:1–29.
- Buckwalter JG, Simpson SW. Psychological factors in the etiology and treatment of severe nausea and vomiting in pregnancy. *American Journal of Obstetrics & Gynecology*. 2002; 186:S210–S214. [PubMed: 12011888]
- Cyranowski JM, Hofkens TL, Frank E, Seltman H, Hoe-Ming C, Amico JA. Evidence of dysregulated peripheral oxytocin release among depressed women. *Psychosomatic Medicine*. 2008; 70:967–75.
- Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, Franks AL. Hospitalizations during pregnancy among managed care enrollees. *Obstetrics & Gynecology*. 2002; 100:94–100. [PubMed: 12100809]
- Heim C, Young LJ, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. Lower CSF oxytocin concentrations in women with a history of childhood abuse. *Molecular Psychiatry*. 2009; 14:954–958. [PubMed: 18957940]
- Hurlemann R, Patin A, Onur OA, Cohen MX, Baumgartner T, Metzler S, et al. Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *Journal of Neuroscience*. 2010; 30:4999–5007. [PubMed: 20371820]
- Kilpatrick, DG.; Resnick, HS.; Freedy, JR.; Pelcovitz, D.; Resick, P.; Roth, S.; van der Kolk, B. *DSM-IV Sourcebook*. Washington, DC: American Psychiatric Press; 1994. The posttraumatic stress disorder field trial: Emphasis on Criterion A and overall PTSD diagnosis.
- Koren G, Boskovic R, Hard M, Maltepe C, Navioz Y, Einarson A. Motherisk—PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy. *American Journal of Obstetrics & Gynecology*. 2002; 186:S228–231. [PubMed: 12011891]
- Liberzon I, Young EA. Effects of stress and glucocorticoids on CNS oxytocin receptor binding. *Psychoneuroendocrinology*. 1997; 22:411–22. [PubMed: 9364620]
- Maes M, Lin A, Bonaccorso S, Goossens F, Van Gastel A, Pioli R, et al. Higher serum prolactin endopeptidase activity in patients with post-traumatic stress disorder. *Journal of Affective Disorders*. 1999; 53:27–34. [PubMed: 10363664]
- Nijenhuis ER, van Dyck R, ter Kuile MM, Mourits MJ, Spinhoven P, van der Hart O. Evidence for associations among somatoform dissociation, psychological dissociation and reported trauma in patients with chronic pelvic pain. *Journal of Psychosomatic Obstetrics and Gynaecology*. 2003; 24:87–98. [PubMed: 12854393]
- Nyquist H. Certain topics in telegraph transmission theory. *trans AIEE*. 1928; 47:617–644.
- Pedersen, C.; Caldwell, J.; Jirikowski, G.; Insel, T., editors. *Oxytocin in maternal, sexual, and social behaviors*. New York: The New York Academy of Sciences; 1992. p. 652
- Pitman RK, Orr SP, Lasko NB. Effects of Intranasal Vasopressin and Oxytocin on Physiologic Responding During Personal Combat Imagery in Vietnam Veterans with Posttraumatic Stress Disorder. *Psychiatry Research*. 1993; 48:107–117. [PubMed: 8416021]
- Porges, SW. *The Polyvagal Theory*. New York: W.W. Norton & Co., Inc; 2011.
- Schore, AN. *Affect dysregulation and disorders of the self*. New York: W.W. Norton & Co., Inc; 2003.
- Seng JS, Oakley DJ, Sampselle CM, Killian C, Graham-Bermann S, Liberzon I. Association of posttraumatic stress disorder with pregnancy complications. *Obstetrics & Gynecology*. 2001; 97:17–22. [PubMed: 11152900]

- Seng JS, Clark MK, McCarthy AM, Ronis DL. PTSD and physical co-morbidity among women: Results from service use data. *Journal of Traumatic Stress*. 2006; 19:45–56. [PubMed: 16568470]
- Seng JS, Schrot J, van de Ven CJM, Liberzon I. Service use data analysis of pre-pregnancy psychiatric and somatic diagnoses in women with hyperemesis gravidarum. *Journal of Psychosomatic Obstetrics and Gynaecology*. 2007; 28:209–17. [PubMed: 17852658]
- Seng JS. Is posttraumatic oxytocin dysregulation a link among posttraumatic self disorders, posttraumatic stress disorder, and pelvic visceral dysregulation conditions in women? *Journal of Trauma & Dissociation*. 2010; 11:387–406. [PubMed: 20938865]
- Taylor SE, Gonzaga GC, Klein LC, Hu P, Greendale GA, Seeman TE. Relation of oxytocin to psychological stress responses and hypothalamic-pituitary-adrenocortical axis activity in older women. *Psychosomatic Medicine*. 2006; 68:238–245. [PubMed: 16554389]
- Teicher MH, Anderson SL, Polcari A, Anderson CM, Navalta CP. Developmental neurobiology of childhood stress and trauma. *Psychiatric Clinics of North America*. 2002; 25:397–426. [PubMed: 12136507]
- Uvnäs-Moberg, K. The oxytocin factor: Tapping the hormone of calm, love, and healing. Cambridge (MA): Da Capo Press; 2003.
- Waller NG, Carlson EB, Putnam FW. Types of dissociation and dissociative types: A taxometric analysis of dissociative experiences. *Psychological Methods*. 1996; 1:300–321.
- Walsh JW, Hasler WL, Nugent CE, Owyang C. Progesterone and estrogen are potential mediators of gastric slow-wave dysrhythmias in nausea of pregnancy. *American Journal of Physiology*. 1996; 270:G506–14. [PubMed: 8638718]
- World Health Organization. The ICD-10 Classification of Mental and Behavioral Disorders. Geneva: WHO; 2007 version
- Wolfe, J.; Kimerling, R. Gender issues in the assessment of posttraumatic stress disorder. In: Wilson, JP.; Keane, TM., editors. *Assessing psychological trauma and PTSD*. New York: Guilford Press; 1997. p. 192-238.

Figure 1.
Estimated marginal means of oxytocin level across case and control groups by dissociation level.

Table 1

Descriptive profile for the overall sample with tests for differences among the four groups.

Characteristic	Total, n=25	NV only, n=9	HG only, n=6	NV and PTSD, n=5	HG and PTSD, n=5	p
	% (n) or mean (SD)					
Protocol						
Pilot protocol B	40.0% (10)	33.3% (3)	33.3% (2)	60.0% (3)	40.0% (2)	.774
Demographics						
African American	44.0% (11)	77.8% (7)	33.3% (2)	0.0% (0)	40.0% (2)	.038
Low education	72.0% (18)	77.8% (7)	83.3% (5)	40.0% (2)	80.0% (4)	.358
Poverty	16.0% (4)	0.0% (0)	33.3% (2)	20.0% (1)	20.0% (1)	.365
Teen	20.0% (5)	33.3% (3)	33.3% (2)	0.0% (0)	0.0% (0)	.244
Pregnancy factors						
First infant	52.0% (13)	44.4% (4)	66.7% (4)	60.0% (3)	40.0% (2)	.768
Mean gestational age	12.2 (2.7)	12.2 (2.7)	12.7 (3.4)	11.4 (1.5)	12.2 (3.4)	.909
Mean beta HcG, mIU/ml	83,297 (43,879)	71,230 (32,915)	126,659 (44,122)	50,365 (24,486)	97,407 (46,814)	.019
Mean estradiol, pg/mL	2,937 (2,095)	2,548 (1,192)	4,713 (2,919)	1,484 (789)	3,410 (2,584)	.077
Mean progesterone, ng/mL	30.0 (13.9)	27.2 (7.9)	43.6 (21.5)	23.8 (14.6)	31.0 (11.0)	.157
Trauma History						
Childhood abuse/neglect	28.0% (7)	11.1% (1)	0.0% (0)	60.0% (3)	60.0% (3)	.034
Adult abuse/assault	40.0% (10)	22.0% (2)	0.0% (0)	80.0% (4)	80.0% (4)	.008
Mean sum of trauma exposures	6.6 (3.6)	5.3 (3.0)	6.3 (2.4)	6.2 (3.9)	9.6 (4.5)	.194
Mental Health						
PTSD score mean	5.5 (4.8)	1.8 (1.8)	3.3 (2.9)	8.2 (2.4)	12.0 (3.7)	<.001
Dissociation score mean	10.0 (2.9)	8.6 (1.1)	10.3 (2.3)	9.4 (1.5)	12.6 (5.1)	.079
Dissociation "case" (>median)	36.0% (9)	22.2% (2)	50.0% (3)	20.0% (1)	60.0% (3)	.383
Nausea and vomiting						
PUQE score mean	8.0 (3.6)	5.7 (2.4)	11.0 (2.4)	5.1 (1.3)	11.3 (2.9)	<.001
Using antiemetic	28% (7)	0.0% (0)	83.3% (5)	0.0% (0)	40.0% (2)	.002

df = 3 for chi squared tests; df = 3, 21 for ANOVAs except for pregnancy hormones where there is missing data for two women, and df = 3, 19.

Table 2

Tests by ANOVA with effect size estimations, followed by additional tests of the *post hoc* hypothesis that it is dissociation, rather than PTSD *per se* that is predictive of oxytocin concentration.*

HG Subtypes		PUQE score	ANOVA
NV only	n=9	5.7 (2.4)	F = 12.1
HG only	n=6	11.0 (2.4)	df = 3,21
NV and PTSD	n=5	5.1 (1.3)	p = <.001
HG and PTSD (posttraumatic HG)	n=5	11.3 (2.9)	Eta ² = .634

HG Subtypes		Dissociation score	ANOVA
NV only	n=9	0.6 (1.1)	F = 2.6
HG only	n=6	2.3 (2.3)	df = 3,21
NV and PTSD	n=5	1.4 (1.5)	p = .079
HG and PTSD (posttraumatic HG)	n=5	4.6 (5.1)	Eta ² = .271

HG Subtypes		Oxytocin, pg/mL	ANOVA
NV only	n=9	114.9 (50.9)	F = 2.6
HG only	n=6	138.4 (88.7)	df = 3,21
NV and PTSD	n=5	159.7 (61.6)	p = .078
HG and PTSD (posttraumatic HG)	n=5	443.8 (171.8)	Eta ² = .272

Psychiatric Subtypes		Oxytocin, pg/mL	ANOVA
Neither PTSD nor Dissociation	n=10	117.9 (142.0)	F = 10.9
PTSD only	n=6	72.0 (41.8)	df = 3,21
Dissociation only	n=5	162.6 (172.5)	p < .001
Both PTSD and Dissociation	n=4	619.8 (290.0)	Eta ² = .610

*eta² estimates proportion of variance explained

Table 3

Regression models testing the hypotheses.

a) Model testing that the HG and PTSD subtype is uniquely associated with log-transformed noon oxytocin level.				
		Standardized Coefficients	t	Sig.
		Beta		
1	HG only (n = 6)	.219	1.048	.306
	NV and PTSD (n = 5)	.041	.197	.845
	HG and PTSD (n = 5)	.558	2.693	.014

b) Stepwise model testing that dissociation mediates the association of posttraumatic HG with log-transformed noon oxytocin level				
		Standardized Coefficients	t	Sig.
		Beta		
1	HG and PTSD (n = 5)	.486	2.668	.014
2	HG and PTSD (n = 5)	.282	1.501	.148
	DES-T score	.439	2.335	.029

Adjusted R-squared = .172

Adjusted R-squared step 1 = .203

Adjusted R-squared step 2 = .332

Results of general linear model of the four-group variable, dissociative median split variable, and their interaction to estimate effect sizes and observed power in relation to noon oxytocin level.

Table 4

	df	F	Sig.	Partial Eta Squared	Observed Power
Corrected Model	7	4.656	.005	.657	.951
Intercept	1	747.519	.000	.978	1.000
Four HG x PTSD groups	3	4.309	.020	.432	.773
Dissociation median split groups	1	8.064	.011	.322	.763
Four groups x Dissociation interaction	3	4.671	.015	.452	.808

Adjusted R Squared = .516