Perinatal Depressive Symptoms: A Search for a Biologic Marker

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THESIS

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This thesis is dedicated to my family. My husband Dave and my two children, Ethan and Sophia who were born during this doctorate. I love you all so much and without your patience and support this would never have been accomplished.

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SUMMARY

Two secondary analyses were completed regarding perinatal depressive symptoms using the Biopsychosocial Model.

The first secondary analysis examined the relationships among biological factors, psychological status, health behaviors, life stress, neuroendocrine mechanisms, and postpartum depressive symptoms. In this secondary analysis, data originated from 113 postpartum low-income mothers with low birth weight infants in the Neonatal Intensive Care Unit (NICU). Maternal demographics, medical history, and self-administered psychological instruments were obtained from the parent study. A sub-sample of 9 women also provided four saliva and blood samples for the measurement of cortisol (saliva) and oxytocin (plasma). Increased postpartum depressive symptoms were related to lower infant birth weight, more severe infant illness, increased posttraumatic stress symptoms, increased anxiety, and increased parental stress. In the sub-sample, cortisol had a dysregulated 24-hour pattern, while oxytocin was inversely related to posttraumatic stress symptoms and anxiety. Though much is known about the adverse outcomes of elevated postpartum depressive symptoms, little is known about the relationship among posttraumatic stress, postpartum depressive symptoms, and neuroendocrine mechanisms. Future research should include assessment of posttraumatic stress, anxiety, and neuroendocrine mechanisms for mothers at risk for elevated postpartum depressive symptoms including those who deliver premature infants.

The second secondary analysis examined the relationships among contributing factors, oxytocin, and prenatal depressive symptoms. In this secondary analysis, data from 57 pregnant African American women residing in an urban setting were analyzed. Maternal demographic information, a medical history review, self-administered psychological instruments, and plasma oxytocin levels were obtained at two time points

during pregnancy, 15 – 22 weeks gestation and 25 – 37 weeks gestation, with an additional medical record review after birth. Oxytocin was inversely related to prenatal depressive symptoms and infant birth weight. Previous obstetrical complications, increased maternal age, and smoking were related to a decrease in oxytocin between the second and third trimester of pregnancy. Women with less family support, a current obstetrical complication, and a previous medical diagnosis were at risk for elevated prenatal depressive symptoms.   Although the data suggest that oxytocin may be a potential biomarker to help identify women at risk for prenatal depressive symptoms, future research is warranted to confirm these results

I. TESTING THE BIOPSYCHOSOCIAL MODEL FOR POSTPARTUM DEPRESSIVE SYMPTOMS IN LOW INCOME WOMEN WITH A LOW BIRTH WEIGHT PREMATURE INFANT

A.   Introduction

Approximately 19% of postpartum women experience a major depressive episode within three months of giving birth (Gavin et al., 2005). In low income mothers up to 48% report elevated postpartum depressive symptoms (Chung, McCollum, Elo, Lee, & Culhane, 2004). Mothers with elevated postpartum depressive symptoms are less responsive and engage in fewer social behaviors, resulting in more difficult mother-infant interactions than mothers without elevated postpartum depressive symptoms (McIntosh, Stern, & Ferguson, 2004; McLearn, Minkovitz, Strobino, Marks, & Hou, 2006; Poehlmann & Fiese, 2001). Elevated postpartum depressive symptoms have been linked with failure to thrive (Lyons-Ruth, Zoll, Connell, & Grunebaum, 1986; Martins & Garffan, 2000; Patel, Rahman, Jacob, & Hughes, 2004), increased risk for developmental delays, and difficulty with social interaction in the infants (Murray & Cooper, 1997). The constellation of biological factors, psychological status, health behaviors, life stress, and neuroendocrine mechanisms that place low-income mothers with premature infants at risk for postpartum depressive symptoms remains unknown. Thus, methods to identify women at risk for postpartum depressive symptoms have not been effective or routinely used in clinical practice. The purpose of this study was to identify the constellation of factors related to postpartum depressive symptoms in low-income mothers with premature infants in the Neonatal Intensive Care Unit (NICU).

Mothers with elevated postpartum depressive symptoms experience unbearable loneliness, thoughts of being a bad mother, guilt over their thoughts, uncontrollable anxiety, and overwhelming feelings of insecurity (Beck, 1992). Additionally, these

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mothers exhibit fewer social behaviors (e.g., less talking to the infant and less play) leading to mother-infant interaction difficulties than mothers without elevated depressive symptoms (McIntosh et al., 2004; McLearn et al., 2006; Poehlmann & Fiese, 2001). In low income communities, mothers with elevated postpartum depressive symptoms were more likely to have a hospitalized child, use corporal punishment, and fail to follow the back-to-sleep recommendations than mothers without elevated symptoms (Chung et al., 2004). When compared with mothers of healthy full term infants, mothers of premature infants were at a greater risk for elevated postpartum depressive symptoms (Davis, Edwards, Mohay, & Wollin, 2003; Miles, Holditch-Davis, Schwartz, & Scher, 2007). This increased risk may be due to the stress of a premature delivery and the responsibility of parenting a premature infant (Davis et al., 2003; Driscoll, 2006; Feeley et al., 2011; Foster, Bidewell, Buckmaster, Lees, & Henderson-Smart, 2008; Franck, Allen, Cox, & Winter, 2005; Miles et al., 2007; Olshtain-Mann & Auslander, 2008). For parents, the stress of having a premature infant may include stress associated with the infant appearance and behavior, parental role in the NICU, the NICU environment and routines, relationships with NICU staff, and the possibility that their infant may have continued health concerns and developmental delays (Davis et al., 2003; Miles, Funk, & Carlson, 1993).

Healthy infants of mothers with elevated postpartum depressive symptoms exhibit less engaging interactive behavior, lower concentration, and less social ability when interacting with strangers when compared with infants of non-depressed mothers (Stein et al., 1996). Failure to thrive, increased risk for developmental delays, and altered social interaction skills have been reported in infants whose mothers have elevated postpartum depressive symptoms as well (Lyons-Ruth et al., 1986; Martins & Garffan, 2000; Murray & Cooper, 1997; Patel et al., 2004). In low income communities, the children of mothers with elevated postpartum depressive symptoms visited

emergency departments and pediatricians more often for sick child appointments, yet had a decreased usage of preventative services including well-child visits and up to date vaccinations than low income mothers without elevated depressive symptoms (Minkovitz et al., 2005). Identifying factors related to elevated postpartum depressive symptoms may aid in early identification of these women, increasing treatment, and therefore decreasing negative sequelae for term infants, premature infants, and mothers.

    1.   Contributing Risk Factors

Biological factors such as maternal age, race, genetics, infant birth weight, and infant illness are known risk factors for postpartum depressive symptoms (Caspi et al., 2003; Davis et al., 2003; Howell, Mora, Horowitz, & Leventhal, 2005). African American and Latina women are more likely to report elevated postpartum depressive symptoms than white women (Howell et al., 2005). Anxiety and posttraumatic stress have been identified as co-morbid conditions with depressive symptoms (Bleich, Koslowsky, Dolev, & Lerer, 1997; Dow & Kline, 1997; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Solomon et al., 1991; Zlotnick, Warshaw, Shea, & Keller, 1997). The incidence of post-traumatic stress disorder (PTSD) in obstetrical patients and new mothers ranges from 1.7% to 9% (Beck, Gable, Sakala, & Declercq, 2011; Maggioni, Margola, & Filippi, 2006), with low-income women and women with a premature infant being at an increased risk (Feeley et al., 2011; Rosen, Seng, Tolman, & Mallinger, 2007; Vanderbilt, Bushley, Young, & Frank, 2009). In low-income women with elevated posttraumatic stress symptoms, 66.7% of them also met the criteria for elevated depressive symptoms (Smith, Poschman, Cavaleri, Howell, & Yonkers, 2006). Impaired health behaviors such as difficulty breastfeeding (Watkins, Meltzer-Brody, Zolnoun, & Stuebe, 2011), poor eating habits (Chatzi et al., 2011), and poor sleep quality (Okun et al., 2011) have been linked to elevated depressive symptoms. Lack of social support and parental stress have also been linked to elevated postpartum depressive

symptoms (Beck & Gable, 2001a, 2001b; Kendler, Gardner, & Prescott, 2002;

MacDonald et al., 2005; Straub et al., 1998). Stress may be related other contributing

risk factors including birth of a premature infant (Younger, Kendell, & Pickler, 1997),

genetics (Mitchell et al., 2011), and recreational drug use (Strantz & Welch, 1995). The

bidirectional interactions of potential contributing factors leads to difficulty in identifying a

constellation of risk factors for elevated postpartum depressive symptoms.

2.   Potential Neuroendocrine Mechanisms and Postpartum Depressive

        Symptoms

        Cortisol and oxytocin are two potential biologic markers for postpartum

depressive symptoms and are involved in the stress response and maternal behaviors

respectively. The hypothalamic-pituitary-adrenal (HPA) axis is modulated by stress

(Kirschbaum & Hellhammer, 1994; Levine, Zagoory-Sharon, Feldman, Lewis, & Weller,

2007; McCoy, M., & Watson, 2003; Swaab, Bao, & Lucassen, 2005). The stress

response includes the hypothalamus release of corticotrophin-releasing factor (CRF),

leading to the anterior pituitary release of adrenocorticotropic hormone (ACTH), leading

to the adrenal glands release of cortisol (Swaab et al., 2005). Due to the high levels of

cortisol during labor and birth, cortisol release is suppressed during the immediate

postpartum period, then normalized within the first 12 weeks postpartum (Mastorakos &

Ilias, 2000). Decreased secretion of cortisol in the immediate postpartum period

suppresses ovarian estrogen and progesterone secretion, causing estradiol fluctuations

(Chrousos, Torpy, & Gold, 1998). Estradiol fluctuations in turn create a vulnerability for

mood and autoimmune disorders in all postpartum women creating a vulnerability for

mood disorders (Chrousos et al., 1998). The relationship among cortisol, stress,

physical illness, and mental health have been previously reported (Altemus, Deuster,

Galliven, Carter, & Gold, 1995; Altemus et al., 2001; Gold & Chrousos, 2002; Johnson et

al., 1996; Machatschke, Wallner, Schams, & Dittami, 2004; Nachmias, Gunnar,

Mangelsdorf, Parritz, & Buss, 1996; Ramsay & Lewis, 2003; Redwine, Altemus, Leong, & Carter, 2001). In very low-income depressed women, cortisol may have a blunted response to stressors, including a decrease in cortisol output when the HPA axis is stimulated (Burke, Fernald, Gertler, & Adler, 2005; Peeters, Nicholson, & Berkhof, 2003). The relationship between cortisol levels and postpartum depressive symptoms has conflicting findings such that researchers have identified direct relationships, inverse relationships, and no relationships (Fugate Woods et al., 2008; Hendrick, Altshuler, & Suri, 1998; Jolley, Elmore, Barnard, & Carr, 2007; McCoy et al., 2003). These conflicting results may be due to a dysregulated HPA axis as evidenced by women with elevated postpartum depressive symptoms exhibiting a higher ACTH levels and lower cortisol levels than women without elevated depressive symptoms (Jolley et al., 2007).

Oxytocin is a hormone and neurotransmitter (Larsen, Kronenberg, Melmed, & Polonsky, 2003). Central oxytocin release targets neurons with signaling effects on behavior and on peripheral oxytocin release, though oxytocin does not cross the blood/brain barrier (Larsen et al., 2003; Speroff & Fitz, 2005). Oxytocin release can be stimulated by social interactions, vaginal stimulation, labor progression, and lactation (Larsen et al., 2003; Speroff & Fitz, 2005; Uvnas-Moberg, 2003). The significance of oxytocin in the birthing process, lactation, and maternal behaviors supports the hypothesis that oxytocin may be related to postpartum depressive symptoms due to its importance in initiating the previous behaviors. Because there is an inverse relationship between oxytocin and cortisol, measuring both of these biologic markers may provide more information about alterations in neuroendocrine mechanisms in women with elevated postpartum depressive symptoms (Kirschbaum & Hellhammer, 1994).

The Biopsychosocial Model for Postpartum Depressive Symptoms guided this study. This model includes a constellation of biological factors (age, race, maternal medical history, and infant illness), psychological status (anxiety and posttraumatic

stress symptoms), <u>health behaviors</u> (breastfeeding, education), and <u>life stress</u> (baby's father involvement, income, employment, and parental stress), which effect <u>neuroendocrine mechanisms</u> (measured by cortisol and oxytocin), leading to <u>postpartum depressive symptoms</u>. Biological factors, psychological status, health behaviors, and life stress are grouped together and termed <u>contributing factors</u>. Contributing factors are variables that may influence whether women are at risk of postpartum depressive symptoms. These contributing factors have been previously associated with postpartum depressive symptoms individually, though the biological pathway is not fully understood.

This study tested the Biopsychosocial Model for Postpartum Depressive Symptoms in low-income mothers who had an infant cared for in the Neonatal Intensive Care Unit (NICU). The study attempted to determine: 1) the relationship between contributing factors and postpartum depressive symptoms, and 2) the relationships of cortisol and oxytocin with contributing factors and postpartum depressive symptoms.

B.   <u>Methods</u>

1.   <u>Design</u>

This pilot was part of a secondary analysis of a larger protocol entitled *Mother Administered Interventions for Neonates* (RO1NR009418, Holditch-Davis, D.). Eligibility criteria included the ability to speak and understand English, maternal age greater than 17, and delivery of a premature infant in the NICU weighing less than 1850 grams. Maternal exclusion criteria included a history of HIV, psychosis, or bipolar disease; current diagnosis of major depression; or ongoing critical illness as these circumstances may confound study results. Neonates had to be clinically stable and without symptoms of drug exposure, no congenital neurological anomalies, and not currently receiving mechanical ventilation.

Data were collected on three non-consecutive days. Day 1 (D1) was at time of enrollment into the parent study, Day 2 (D2) was the day of oxytocin collection at the hospital, and cortisol collection at home occurred on the following day after oxytocin collection and is labeled as Day 3 (D3). Day 1 data were collected by the parent study and included questionnaires and self-administered psychological instruments. Day 2 and Day 3 data were only collected from a sub-sample of participants who provided biomarker samples (n = 9).

2.   Setting/Sample

The participants from the parent study included 113 mothers from two hospitals in Chicago. Seventy-six participants were enrolled from a tertiary county hospital and 37 participants were enrolled from a community hospital. Data at D1 were collected by the parent study and participants were instructed to maintain usual behaviors such as not refraining from sexual behavior including breast stimulation or habitual habits such as smoking, drinking, or drug use.

Nine participants were included in the sub-sample. For collection of oxytocin (D2) and cortisol (D3) mothers were instructed to refrain from smoking, recreational drug use, and consumption of large meals immediately prior to data collection. Sexual activity or breastfeeding was not restricted on any day.

3.   Measures

a.   Contributing factors

Contributing factors included biological factors (maternal age, race, infant birth weight, and severity of the infant's illness), psychological status (anxiety and posttraumatic stress symptoms), health behaviors (breastfeeding and education), and life stress (mother not living with the baby's father and parental stress).

i.   <u>Biological factors</u>

Biological Factors included maternal age, race, infant birth weight, and severity of the infant's illness. Maternal age, race, and infant birth weight were obtained through infant medical records. Severity of the infant's illness was assessed using the Neurobiologic Risk Score (NBRS). The NBRS is a 7-item assessment of potential insults to an infant's brain that correlate to development at 6, 15, and 24 months (Brazy, Goldstein, Oehler, Gustafson, & Thompson, 1993). Each item is ranked by severity on a 4-point geometric grade (0, 1, 2, 4).   Scores on the NBRS correlate between -0.37 and 0.76 with the Bayley (mental (MDI) and psychomotor developmental indices (PDI)) and neurologic examinations (Brazy, Eckerman, Oehler, Goldstein, & O'Rand, 1991). The Cronbach's alpha for the sample in the larger study was 0.71. Low risk was determined as a score ≤ 4, intermediate was 5 - 7 and high risk was greater ≥ 8 (Brazy et al., 1993).

ii.   <u>Psychological status</u>

Psychological status was assessed through a woman's current state anxiety level and posttraumatic stress symptoms. Anxiety has been described along a continuum as normal tension or fear continuing to anxiety that affects functions of daily life (Frisch & Frisch, 2002). Symptoms of anxiety include restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disorders (Frisch & Frisch, 2002). Current state anxiety was measured using the state portion of the self-administered State-Trait Anxiety Inventory (STAI) (Kendall, Finch, Auerbach, Hooke, & Mikulka, 1976; Ramanaiah, Franzen, & Schill, 1983; Spielberger, Auerbach, & Wadsworth, 1970). The state subscale of the STAI consisted of 20 items rated on a 4-point Likert scale and included topics such as the degree to which the mother currently felt happy, calm, comfortable, jittery, upset, and confused. The Cronbach's alpha ranges from 0.85 to 0.95 (Catlett, Miles, & Holditch-Davis, 1994), and for the sample of the

larger study was 0.93. Although there is no cutoff value, a higher score is associated with higher anxiety (Spielberger, 1983).

Posttraumatic Stress Disorder (PTSD) is a specific type of anxiety disorder affecting persons exposed to traumatic events (APA, 2000; Seng, 2003). Elevated posttraumatic stress symptoms are characterized by the three symptoms of PTSD and include: 1) re-experiencing the event through thoughts, 2) avoidance of stimuli related to the event, and 3) increased arousal since the event has occurred (APA, 2000). Posttraumatic stress symptoms were assessed using the Perinatal Post-Traumatic Stress Disorder Questionnaire (PPQ) (Callahan & Borja, 2008; Callahan, Borja, & Hynan, 2006; Callahan & Hynan, 2002; Quinnell & Hynan, 1999) The PPQ is a 14 item yes/no questionnaire with statements including topics about the mother having upsetting memories of giving birth, avoiding thinking about baby's hospital stay, an inability to remember parts of the hospital stay, and difficulty feeling loved. The cutoff for at risk for PTSD is a score of 6 or greater. Cronbach's alpha is reported as 0.83 with a test-retest reliability of 0.92. For the sample of the larger study, the Cronbach's alpha was 0.79.

iii.   Health behaviors

Health behaviors for this study included breastfeeding and education. They were obtained through participant self-administered questions.

iv.   Life stress

Life stress was quantified in this study as whether the mother lived with the baby's father and her parental stress level. Living with baby's father was assessed by a self-administered question. Parental stress was measured using the Parental Stressor Scale: NICU (PSS: NICU). The PSS: NICU consists of two subscales including parental role alteration (12 items) and infant appearance and behavior (16 items). The PSS: NICU uses a 5-point Likert scale ranging from "not at all stressful" to "extremely stressful". Cronbach's alpha was previously reported as 0.88

(Miles et al., 1993). In the total sample from the larger study, the Cronbach's alpha was 0.90 for the parental role alteration subscale and 0.91 for the infant appearance and behavior subscale.

b.	Cortisol

Participants collected salivary samples at four time points throughout the day. Sampling times were based on established circadian rhythm of cortisol release (Kudielka, Gierens, Hellhammer, Wust, & Schlotz, 2012) and included awakening (T1), 30-minutes post awakening (T2), late afternoon (T3), and before bed (T4). Participants were instructed not to consume alcohol or recreational drugs 24 hours prior to collection or consume a large meal one hour before collection. Participants began the collection by washing out their mouths with water, then passively drooling through a straw into the collection container, and placing the samples in their refrigerator until they were picked up the following day. Samples were taken to the laboratory, divided into aliquots, and frozen (-80°C) for batch analysis (Kirschbaum & Hellhammer, 1994; Salimetrics). Cortisol was measured using a commercial enzyme immunoassay kit developed by Salimetrics, LLC (State College, PA). Measurements were performed in duplicate and all samples were assayed in the same batch to avoid inter-assay differences. The inter-assay coefficient of variation reported on the kit is 3.35% and 3.65%, while the intra-assay coefficient of variation is 3.75% and 6.41% and a sensitivity of 0.003 µg/dl.

c.	Oxytocin

To determine oxytocin values, blood was collected at four time points over 50 minutes (T1 = 0 min, T2 = 10 min, T3 = 30 min, T4 = 50 min). The time points were selected to obtain a baseline value, to determine if stress due to venous puncture affected baseline, and to evaluate if a change in oxytocin level was observed when mothers interacted with their infants. Frequent oxytocin sampling was also based

on the short half-life of oxytocin (three to six minutes) (Speroff & Fitz, 2005). T1 and T2 were baseline measurements and obtained outside the NICU in a private family waiting area. T3 and T4 were obtained at the infant's bedside in the NICU. Mothers were encouraged to interact, touch, and talk to their infants between T3 and T4. Blood was collected in test tubes containing the anticoagulant ethylene diamine tetraacetic acid (EDTA).

Samples were immediately placed on ice after each collection. Blood was taken to the laboratory, centrifuged to obtain a plasma sample, which was divided into aliquots, and frozen for batch analysis. Oxytocin was assayed using Assay Designs 96 plate commercial oxytocin ELISA kit. Measurements were performed in duplicate and all samples were assayed in the same batch to avoid inter-assay differences. Oxytocin detection levels were 15.6 pg/ml to 1000 pg/ml with a sensitivity as low as 11.7 pg/ml. Samples were diluted in the assay buffer (ratio of 1:2) and treated according to directions of the kit. Reliable values were considered if coefficient of variance between duplicates was less than 30%. These kits have an intra-assay variance ranging from 8.7% - 12.4% and inter-assay variance ranging from 5.2% - 14.5% (AssayDesigns, 2006).

<div align="center">d.   <u>Postpartum Depressive Symptoms</u></div>

Major Depressive Disorder was defined by the DSM-4, as a Major Depressive Episode not superimposed on another mental disorder and without the occurrence of mania (APA, 2000). A Major Depressive Episode is defined as five or more depressive symptoms present in a two week period, most occurring nearly everyday, and causing an individual impairment with social, occupational, or daily functions (APA, 2000). Postpartum depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CESD). The CESD consists of 20 depressive symptoms rated on a 4-point Likert scale. Scores range from 0 - 60 with a

cut-off value of greater than 16 signifying elevated depressive symptoms (Radloff, 1977). The CESD was not developed to assess postpartum women, yet in the general population it is used widely for screening for Major Depressive Disorder (Chung et al., 2004; Minkovitz et al., 2005; Radloff, 1977). In postpartum women, the CESD had an internal consistency of 0.82, a sensitivity of 60%, and a specificity of 92% (Boyd, Le, & Somberg, 2005). In mothers of preterm and medically fragile infants, CESD Cronbach's alphas were 0.87 - 0.91 (Miles et al., 2007) and in this sample was 0.90. The CESD also has a strong correlation with the Edinburgh Postnatal Depression Scale (EPDS) (r = 0.80, p < 0.01) identifying women with elevated postpartum depressive symptoms (Boyd et al., 2005).

4.   Procedures

The University of Illinois at Chicago Institutional Review Board approved the research protocol. One hundred thirteen postpartum mothers of low birth weight infants in the NICU had completed the parent study and their data were available for secondary analysis. Towards the completion of the parent study, newly enrolled participants were approached to provide saliva and blood samples for cortisol and oxytocin analysis. Nine mothers agreed to be included in the sub-sample. All data and blood samples were de-identified prior to analysis. Saliva and blood samples were processed as described above for cortisol and oxytocin analysis.

5.   Data Analysis

Descriptive statistics were conducted to determine frequencies, means, and ranges for all variables. Cortisol data were graphed for review of potential circadian patterns. All analyses were conducted using two-tailed tests and the level of significance selected was α = 0.05.

The relationships between postpartum depressive symptoms and contributing factors in the total sample (113 women) (Aim 1) were analyzed as follows. Spearman's

Rho correlations were conducted to determine the relationships between postpartum depressive symptoms and maternal age, infant birth weight, infant illness severity, posttraumatic stress symptoms, anxiety, breastfeeding, education, and parental stress. Spearman's Rho correlations were used as a large number of participants were expected to score above the cutoff for clinically significant depressive symptoms, thus approximating a nonparametric distribution. To determine the relationship between postpartum depressive symptoms and race, an ANOVA was conducted with Tukey post-hoc testing. To determine the relationship between postpartum depressive symptoms and living with the baby's father, a *t*-test was conducted. To determine the relationship between contributing factors as a group and postpartum depressive symptoms, a linear regression model using forward stepwise method and a general linear regression model were conducted.

The relationships between cortisol and oxytocin with contributing factors and postpartum depressive symptoms in the sub-sample (*n* = 9) (Aim 2) were analyzed as follows. Spearman's Rho correlations were conducted to determine the relationships between cortisol and oxytocin with postpartum depressive symptoms, maternal age, infant birth weight, infant illness severity, posttraumatic stress symptoms, anxiety, breastfeeding, education, and parental stress. Spearman's Rho correlations were used because of the small sample size in the sub-sample and because a nonparametric distribution of cortisol and oxytocin were expected. To determine the relationship between cortisol and oxytocin with race, an ANOVA was conducted followed by Tukey post-hoc testing. To determine the relationship between cortisol and oxytocin with living with the baby's father, a *t*-test was conducted. Finally, to identify predictors of cortisol and oxytocin, two separate logistic regressions using forward stepwise method were conducted.

C.   Results

1.   Contributing factors

The sample included 113 women aged 18 - 43 years with infants born at 26-34 weeks gestation, weighing 420 grams – 1780 grams. The participant sample was predominately minority including African American (n = 92), Latina (n = 17), and Caucasian (n = 4) mothers. Infant illness, measured by the NBRS, had scores ranging from 0 – 16 with a mean of 3.2 ± 3.1.

Psychological status of the sample included STAI scores (state anxiety), which ranged from 20 – 80 with a mean of 39.1 ± 12.6. Posttraumatic stress symptoms, as measured by the PPQ, ranged from 0 – 11, with a mean of 3.91 ± 3, and 29.6% (n = 33) of the mothers scoring above the cutoff.

Health behaviors included the majority (67.9%, n = 76) of participants providing breast milk for their babies. A small number of participants (11.5%, n = 12) breastfed their infants in the hospital. Education levels varied with 17.6% (n = 19) being without a high-school degree, 42.6% (n = 46) having graduated from high school, 30.6% (n = 33) with some college, and 9.3% (n = 10) being college graduates.

The majority (52.3%, n = 58) of participants did not live with the baby's father. The second measure of life stress was parental stress measured by the PSS: NICU. The PSS: NICU parental role scale ranged from 1 – 60 with a mean of 32.5 (average = 2.71) ± 14.8, the infant behavior and appearance scale ranged from 4 – 77 with a mean of 32.59 (average = 2.04) ± 18.3, and the total PSS: NICU mean was 65.06 (average = 2.32) ± 29.9.

2.   Cortisol Distribution

Cortisol values ranged from 0.1 to 33.49 ng/ml (Table 1), and the shape of the 24-hour cortisol curves had no consistent patterns. One participant had a normal circadian pattern with an high morning cortisol (T1), a peak at 30 minutes after

awakening (T2), then a slow decrease by the afternoon (T3), and a nadir in the evening (T4). Examples of the patterns observed included a low morning cortisol (T1), an increase at 30 minutes after awakening (T2), an increase in the afternoon (T3), and a slight decrease at bedtime (T4) (Figure 2). Other participants had a peak T1, a decrease at T2, and the nadir reached at T3, with no change at T4 (Figure 3). Further patterns included a high T1, followed by a decrease at T2, then an increase T3, ending in a nadir at T4 (Figure 4). With these dysregulated patterns, no consistency in patterns, and only 9 participants, cortisol was not used for further analysis.

      3.   <u>Oxytocin</u>

      Of the nine consented participants, eight participants' blood samples were available for oxytocin assay (one mother's blood samples lysed). Oxytocin values ranged from 103 - 4058 pg/ml (Table 3). Four of the 36 samples had a within sample variance greater than 30%. All four of these samples had values less than 250 pg/ml, thus not varying clinically and therefore remaining in the analysis. Five of the 36 values were above the level of oxytocin detection. These values were caped at the level of detection (1000 x 2 = 2000pg/ml) and analysis continued. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that there was no difference between oxytocin values at any of the four time points ($F = 1.271$, $df = 1.045, 6.273$, $p = 0.304$). All other analyses were performed using oxytocin values at T1.

      4.   <u>Postpartum Depressive Symptoms</u>

      CESD scores (measure of postpartum depressive symptoms) ranged from 1 - 51 with a mean of 15.9 ± 11.5. When CESD scores were dichotomized, 42% ($n = 47$) of participants scored above the cutoff, indicative of elevated postpartum depressive symptoms.

5.   Contributing Factors and Postpartum Depressive Symptoms

Relationships were identified between increased postpartum depressive symptoms and lower infant birth weight, more severe infant illness (higher NBRS), increased posttraumatic stress symptoms (higher PPQ), more anxiety (higher STAI), and more parental stress (higher PSS: NICU) (Table 3). Neither race nor living with the baby's father was related to postpartum depressive symptoms. The linear regression stepwise model for postpartum depressive symptoms was fit using posttraumatic stress symptoms (coefficient = 1.590, standard error = 0.274) and state anxiety (coefficient = 0.468, standard error = 0.065). This model had an R = 0.800, and R^2 = 0.64 (standard error = 7.154). A general linear model was fit using posttraumatic stress symptoms, state anxiety, maternal age, whether the participant lived with the baby's father, severity of infant's illness, infant birth weight, race, education, and parental stress. This model had an R = 0.838, and R^2 = 0.703 (standard error = 6.647, Table 4).

6.   Cortisol and Oxytocin with Contributing Factors and Postpartum
        Depressive Symptoms

Cortisol was not included in the following analyses due to the dysregulated patterns observed.

An inverse relationship between oxytocin and posttraumatic stress symptoms (r = -0.770, n = 8, p = 0.026) was identified (Table 5). An inverse trend was identified between oxytocin and state anxiety (r = -0.639, n = 8, p = 0.088). No other relationships between oxytocin were found. A linear regression model was unsuccessful due to the large number of variables and the small sample size of n = 8.

D. Discussion

This report identified four factors that were interrelated. These factors included posttraumatic stress, postpartum depressive symptoms, anxiety, and parental stress.

Elevated posttraumatic stress symptoms were identified in 29.6% of the sample. Postpartum posttraumatic stress was first reported in the1990s (DeMier, Hynan, Harris, & Manniello, 1996). Mothers of premature infant's report experiencing at least one of the following three symptoms of posttraumatic stress: re-experiencing, avoidance, or increased arousal (Holditch-Davis, Bartlett, Blickman, & Miles, 2003). Approximately 53% of mothers with a premature infant experience all three symptoms (Holditch-Davis et al., 2003). The diagnosis of Posttraumatic Stress Disorder (PTSD) has been identified in 15% of women with infants in the NICU (Lefkowitz, Baxt, & Evans, 2010). Additionally, a co-morbid relationship exists between elevated posttraumatic stress and postpartum depressive symptoms in mothers with infants in the NICU (Lefkowitz et al., 2010).

In this sample, a large percentage of mothers (42%) experienced elevated postpartum depressive symptoms. This finding is consistent with previous research, which identified 39% of mothers with medically fragile infants (Cho, Holditch-Davis, & Miles, 2008) and 48% of low-income mothers (Chung et al., 2004) reported elevated depressive symptoms. Due to the large percentage of this sample having elevated depressive symptoms, our findings further support the evidence that low-income mothers of preterm infants are at increased risk for elevated postpartum depressive symptoms. These mothers may also be at risk for other psychological factors such as anxiety. Anxiety also has a co-morbid relationship with elevated postpartum depressive symptoms (Ross, Gilbert Evans, Sellers, & Romach, 2003).

State anxiety was measured by the STAI, which does not distinguish between high or low anxiety. Reported anxiety in this sample was greater when compared to postpartum women of healthy infants (Aktan, 2012), working women (Spielberger, 1983), women with chronic renal failure (Theofilou, 2011), and women with a family history of cancer (Turner-Cobb, Bloor, Whittemore, West, & Spiegel, 2006). However, anxiety

levels in this sample were lower when compared to previous reports of women with fibromyalgia (Menzies, Lyon, Elswick, Montpetit, & McCain, 2011) or in the military (Spielberger, 1983). Therefore we concluded that women in our sample have high levels of anxiety, yet these levels may be usual for mothers whose infants are in the NICU. This conclusion is further supported by previous research finding mothers with infants in the NICU had greater anxiety than mothers of full term infants (Padovani, Carvalho, Duarte, Martinez, & Linhares, 2009).   Specifically, anxiety levels of parents in the NICU are greatest at admission and decrease throughout the infant's NICU stay (Melnyk et al., 2006). Anxiety levels as well as depressive symptoms are related to other biological responses in new mothers, specifically parental stress (Feldman et al., 2009).

Parental stress, in this sample, was lower than that found in other samples of primarily employed and college-educated parents with infants in the NICU (Franck, Cox, Allen, & Winter, 2005). In this sample, parental stress was also lower when compared to mothers of near-term infants receiving supplemental forms of oxygen (Foster et al., 2008). Parental stress in this sample was greater when compared to a multiracial sample of varying socioeconomic status parents with a low birth weight infant in the NICU (Melnyk et al., 2006). Generally, mothers of premature infants in the NICU exhibit greater parental stress through two months after discharge than mothers of full term healthy infants (Olshtain-Mann & Auslander, 2008). The increase in parental stress in mothers with an infant in the NICU should be assessed throughout the NICU experience as well as after discharge. After discharge is particularly important as this is a time when mothers are more at risk for postpartum depressive symptoms (Grazioli & Terry, 2000).

Overall, postpartum depressive symptoms were related to several factors including infant birth weight, infant illness severity, parental stress, posttraumatic stress, and anxiety. Posttraumatic stress symptoms and anxiety had the greatest association with postpartum depressive symptoms. This finding was consistent with previous

reports of the comorbid relationships between postpartum depressive symptoms, posttraumatic stress, and anxiety (Lefkowitz et al., 2010; Ross et al., 2003). Screening mothers for posttraumatic stress, anxiety, and postpartum depressive symptoms may more accurately identify mothers at risk, and aid in early treatment to potentially decrease negative sequelae. Understanding the neuroendocrine mechanisms occurring with postpartum depressive symptoms, may lead to identification of a diagnostic biologic marker.

1.   Sub-sample Results

The subsample included 9 women from the sample who provided specimens for oxytocin and cortisol data. To our knowledge, this was the first study to explore postpartum serial blood draws for the purpose of detecting possible oxytocin pulses in postpartum mothers of premature infants in the NICU. Oxytocin released during pregnancy and lactation has a pattern of spikes due to its increased pulsatile release (Ludwig & Leng, 2006). In order to determine if one of these spikes occurred, serial measures of oxytocin were needed. When analyzing the four time points, no significant difference in oxytocin values were observed. Future research is needed with a larger sample size and varying methodology of sampling times for oxytocin to confirm whether serial or one-time sampling is adaquate. A one-time sample of oxytocin may be sufficient, though more research on the effects of the postpartum time period and oxytocin spikes are needed.

It has been previously hypothesized that an inverse relationship exists between postpartum posttraumatic stress and oxytocin levels (Seng, 2010). We are the first to identify this potential relationship. Similarly, a trend was identified between oxytocin and anxiety, though the lack of significance may be due to the small sample size ($n = 8$). In estrogen-treated female mice and rats, oxytocin has anxiolytic properties (Gimpl & Fahrenholz, 2001; Neumann, Torner, & Wigger, 2000). In humans, nasal oxytocin

administration immediately prior to a stressful event decreased anxiety compared to placebo administration (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). The mechanism of the anxiolytic effect is currently being explored in animal models (Blume et al., 2008; Okimoto et al., 2012).

We hypothesized that oxytocin was related to other factors including breastfeeding, parental stress, and postpartum depressive symptoms. Women who breastfed immediately prior to a stressful event had an attenuated stress response exhibited by a decreased cortisol level when compared to lactating women who did not breastfeed immediately prior to a stressful event (Heinrichs et al., 2001). Oxytocin's involvement in lactation and the let down reflex has been extensively studied (Gimpl & Fahrenholz, 2001; Uvnas-Moberg, 2003). In lactating women, oxytocin levels are the highest before feeding, then decrease during feeding, and increase again 30 minutes post feeding (White-Traut et al., 2009). In this study, participants did not breastfeed or pump immediately prior or after blood sampling for oxytocin, which may explain why no relationship was identified between breastfeeding and oxytocin.

Animal models demonstrate a relationship between chronic pregnancy stress and oxytocin expression (Hillerer, Reber, Neumann, & Slattery, 2011; Holt-Lunstad, Birmingham, & Light, 2011). Intranasal administration of oxytocin in human models shows an inhibitory stress response (Heinrichs et al., 2003). In this study however, we identified no relationships between parental stress and oxytocin, possibly due to the homogeneity of the participants' parental stress level. Identifying a relationship between oxytocin and parental stress may emerge when mothers of premature infants in the NICU are compared to mothers of healthy full-term infants.

In this sample, an inverse relationship between oxytocin and postpartum depressive symptoms was hypothesized, though no relationship was identified. In a sample of non-pregnant women, those with increased depressive symptoms had

decreased oxytocin levels (Scantamburlo et al., 2007). Women with depressive

symptoms have also exhibited a dysregulated oxytocin release with more frequent

pulses than women without elevated symptoms (Cyranowski et al., 2008). Mothers who

exhibited high levels of affectionate contact with their infant had an increase in oxytocin

level after the mother-infant interaction (Feldman, Gordon, Schneiderman, Weisman, &

Zagoory-Sharon, 2010). Oxytocin release has strong relationships with social behaviors

(Gimpl & Fahrenholz, 2001). Previous research with larger samples suggested the

potential for oxytocin to be a potential biologic marker for postpartum depressive

symptoms.   Though this study did not identify a relationship between oxytocin and

postpartum depressive symptoms, with the small sample size and specific sample

studied, this relationship warrants further investigation to confirm or negate a

relationship.

Oxytocin inhibits the HPA axis and cortisol release (Neumann et al., 2000). High

oxytocin and low cortisol levels predict nurturing maternal behaviors such as gaze,

affect, touch, and vocalization during the first month postpartum (Feldman, Weller,

Zagoory-Sharon, & Levine, 2007). In our sample, cortisol patterns were dysregulated in

the majority of participants. Cortisol is affected by many variables including exposure to

an acute stressor at collection, smoking, food intake, time of awakening, and mood

(Kudielka et al., 2012). The dysregulated patterns of cortisol may be due to depressive

symptoms (42%), posttraumatic stress (29.6%), dysregulated sleeping and eating

patterns, or other contributors that may be inherent to low-income mothers of infants in

the NICU. Further research on cortisol in this population is warranted to adequately

interpret and understand cortisol levels.

Limitations of this study included a small sample size, decreased generalizability

of results, and method of oxytocin data collection. The small sample size, especially in

the sub-sample (n = 9) was partly due to methodological issues. Recruitment limitations

were based on infant illness (respiratory support was an exclusion criteria), mothers'
limited transportation to the medical centers, and participant burden. The sample of only
urban low-income women with a premature infant in the NICU limits the generalizability
of the results to other groups of mothers. Currently there is no standard oxytocin
collection method in postpartum or lactating women. This method of oxytocin collection
needs further development to ensure the validity of the relationships identified when
using a one-sample approach. Larger studies of oxytocin levels in postpartum women
when they are thinking about their infants, close to their infants, or touching their infants
would further identify how often a pulse in plasma oxytocin levels may be collected. The
probability of measuring an oxytocin pulse instead of a baseline value and the precise
timing between stimulus occurrence and oxytocin release remains unknown. Due to
these unknown characteristics of oxytocin, serial blood sampling is frequently the
method of oxytocin collection. Yet, serial blood sampling puts added burden and
discomfort on participants. With added knowledge of oxytocin characteristics,
determining if a one-time sample is adequate may increase the feasibility of oxytocin
research.

Because this is the first study to identify relationships among posttraumatic
stress, postpartum depressive symptoms, anxiety, and oxytocin, future research on
these factors is warranted. Research including mothers of healthy term, late preterm,
and very low birth weight infants of varying socioeconomic status may lead to more
generalizable results as our sample included only drew participants from a specific
postpartum population. Additional research with new mothers that includes postpartum
posttraumatic stress will add to our understanding of this psychological indicator. Future
research on cortisol in low-income women with a premature infant may include blood as
well as saliva sampling to better understand dysregulated circadian patterns. Cortisol
levels in blood can be directly compared to other biologic markers.   Although we found

little variation between oxytocin levels over a one-hour period (four samples), improved methods of oxytocin collection need further refinement. The relationship identified between oxytocin and postpartum posttraumatic stress as well as the trend with anxiety suggests that oxytocin may be a biologic marker for multiple postpartum mood disorders. Additional research with a larger sample size is required to validate these findings. Research including additional neuroendocrine mechanisms and psychological factors may be useful in identify a constellation of biologic markers that identify new mothers at risk for psychological illness. Future research on posttraumatic stress, postpartum depressive symptoms, anxiety, and oxytocin will aid in early identification and treatment of new mothers, thus decreasing negative sequelae for mothers and infants.

The findings of this study may have implications for clinical practice. The large number of participants identified with elevated posttraumatic stress and postpartum depressive symptoms show the importance of screening all low-income mothers who deliver a premature infant. Elevated posttraumatic stress and postpartum depressive symptoms negatively affect mothers and their infants (Feeley et al., 2011; Minkovitz et al., 2005; Murray & Cooper, 1997). Screening mothers for posttraumatic stress and postpartum depressive symptoms as well as assessing oxytocin levels may identify more mothers at risk, aid in more women getting treatment and improve the outcomes for postpartum women and their infants. Screening can be accomplished by asking mothers questions about their pregnancy, mood, and birth experience and using standardized screening instruments. Oxytocin has the potential to be a biologic marker in assessment for postpartum women at risk for posttraumatic stress and postpartum depressive symptoms. Identification of new mothers with posttraumatic stress or postpartum depressive symptoms is imperative to improve maternal mental health, mother-infant interactions, and infant development thereby reducing negative sequelae.

E.   Tables and Figures

TABLE I: CORTISOL (NG/ML)

Participant #	Awakening	30 min later	1600-1800	Hour of Sleep
1	23.06*	17.62	33.49*	Missing
2	1.89	2.48	3.68*	3.02*
3	2.27	1.80	1.65*	1.53*
4	3.55	2.96	0.73	0.74*
5	1.26	4.52	4.71*	0.1
6	10.74*	9.87	12.09*	2.91*
7	0.73**	0.33	0.33	0.48*
8	5.67	5.16	0.49	0.81*
9	1.97	3.64	0.94	Missing

*   = Elevated cortisol (dependent on diurnal rhythm)
** = Decreased cortisol (dependent on diurnal rhythm)

TABLE II: OXYTOCIN (PG/ML)

Participant #	T1: 0 min	T2: 10 min	T3: 30 min	T4: 50 min
1	188.8	276.5	335.2	240.2
2	3080.0*	2002.0*	1950.0*	1698.0*
3	197.8	216.0	157.2	130.0
4	2448.0*	4058.0*	2697.0*	1798.0*
5	343.4	380.0	382.0	326.0
6	291.6	426.0	234.2	278.0
7	Lysed			
8	181.2	236.0	2100.0*	190.0
9	103.6**	122.0**	Feeding infant	152.0

* = Elevated oxytocin (>800 pg/ml)
** = Decreased oxytocin (<125 pg/ml)

TABLE III: SPEARMAN'S CORRELATIONS
CONTRIBUTING FACTORS AND POSTPARTUM DEPRESSIVE SYMPTOMS

	Infant birth weight	Infant illness severity	Breast feeding (times)	Education (years)	Post-traumatic stress (PPQ)	State anxiety (STAI)	Parental stress (PSS: NICU)	Depressive symptoms (CESD)
Maternal age	*r* = 0.015 *n* = 113	*r* = -0.008 *n* = 114	*r* = -0.119 *n* = 104	*r* = 0.118 *n* = 111	*r* = -0.020 *n* = 111	*r* = 0.045 *n* = 111	*r* = -0.091 *n* = 110	*r* = 0.103 *n* = 111
Infant birth weight		**_r_ = -0.713 ***** *n* = 113	**_r_ = 0.197 **** *n* = 104	*r* = 0.025 *n* = 111	**_r_ = -0.187 **** *n* = 111	**_r_ = -0.267 ***** *n* = 111	*r* = -0.176 *n* = 110	**_r_ = -0.201 **** *n* = 111
Infant illness severity			*r* = -0.137 *n* = 104	*r* = -0.075 *n* = 111	**_r_ = 0.166 *** *n* = 111	**_r_ = 0.305 ***** *n* = 111	**_r_ = 0.319 ***** *n* = 110	**_r_ = 0.276 ***** *n* = 111
Breast feeding				*r* = 0.082 *n* = 102	*r* = -0.119 *n* = 102	*r* = -0.139 *n* = 102	*r* = -0.094 *n* = 101	*r* = -0.107 *n* = 102
Education (years)					*r* = 0.016 *n* = 112	*r* = -0.113 *n* = 112	*r* = -0.036 *n* = 111	*r* = -0.126 *n* = 112
Post-traumatic stress (PPQ)						**_r_ = 0.511 ***** *n* = 112	**_r_ = 0.499 ***** *n* = 111	**_r_ = 0.673 ***** *n* = 112
State anxiety (STAI)							**_r_ = 0.434 ***** *n* = 111	**_r_ = 0.658 ***** *n* = 112
Parental Stress (PSS:NICU)								**_r_ = 0.508 ***** *n* = 111
* = α ≤ 0.1, ****** = α ≤ 0.05, ******* = α ≤ 0.01								

TABLE IV: LINEAR REGRESSION MODEL WITH CONTRIBUTING FACTORS
AND POSTPARTUM DEPRESSIVE SYMPTOMS

Postpartum Depressive Symptoms Primary Aim Results				
R = 0.887, R^2 = 0.703 (standard error = 6.647)				
Model Variable	Coefficients	Standard Error	t	p
Constant	-14.816	5.740	-2.581	**0.011**
PPQ (PTS)	1.449	0.263	5.506	**0.001**
STAI (state anxiety)	0.401	0.063	6.327	**0.001**
Maternal Age	0.361	0.133	2.711	**0.008**
Live with FOB	-3.270	1.330	-2.459	**0.016**
NBRS (infant illness)	0.546	0.272	2.008	**0.047**
Race	-0.861	0.604	-1.426	0.157
Education (years)	-0.255	0.179	-1.422	0.158
PSS: NICU	0.039	0.026	1.509	0.134
Birth weight	0.003	0.002	1.086	0.280

TABLE V: SPEARMAN'S CORRELATIONS
CONTRIBUTING FACTORS AND OXYTOCIN

Postpartum Depressive Symptoms Secondary Aim Correlations	
	Oxytocin at IV insertion (pg/ml) (n = 8)
Maternal age	r = 0.030, p = 0.943
Infant birth weight	r = 0.323, p = 0.435
Infant illness severity	r = -0.012, p = 0.977
Breast feeding (times)	r = 0.579 , p = 0.173
Education (years)	r = 0.251, p = 0.550
Posttraumatic stress symptoms (PPQ)	**r = -0.770, p = 0.026****
Anxiety (STAI)	**r = -0.639, p = 0.088 ***
Parental Stress (PSS)	r = -0.119, p = 0.779
Postpartum Depressive symptoms (CESD)	r = -0.431, p = 0.286
* = α ≤ 0.1, ** = α ≤ 0.05, *** = α ≤ 0.01	

Figure 1: Biopsychosocial Model for Postpartum Depressive Symptoms

Figure 2: 24 Hour Cortisol #1

Figure 3: 24 hour Cortisol #2

Figure 4: 24 hour Cortisol #3

F.   <u>References</u>

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II. EXPLORING THE BIOPSYCHOSOCIAL MODEL OF PRENATAL DEPRESSION AND OXYTOCIN IN AFRICAN AMERICAN WOMEN

A.   Introduction

Approximately 20.4% of pregnant women report elevated prenatal depressive symptoms (Gavin et al., 2005; Marcus, Flynn, Blow, & Barry, 2003; Ventura, Abma, & Mosher, 2008). Women with elevated prenatal depressive symptoms are often undiagnosed and at a greater risk for postpartum depressive symptoms than women without elevated prenatal depressive symptoms (Bowen, Bowen, Butt, Rahman, & Muhajarine, 2012). Women with elevated postpartum depressive symptoms have reported loneliness, thoughts of harming herself or her infant, guilt, and decreased quality of life (Beck, 1992). Prenatal depressive symptoms contribute to altered patterns of mother-infant interactions, such as the mother's lack of desire for close contact with her infant, lack of satisfaction with being a mother, hostility, and feelings of resentment toward her infant (Perry, Ettinger, Mendelson, & Le, 2011). Women with elevated prenatal depressive symptoms are more likely to have a smaller fetus in utero, a premature birth, and low birth weight infants than women without elevated prenatal depressive symptoms (Davalos, Yadon, & Tregellas, 2012; Field, Diego, & Hernandez-Reif, 2006).   Risk factors for prenatal depressive symptoms include young age, being unmarried, being unemployed, smoking, poor overall health, less education, history of depression (Marcus et al., 2003), history of childhood sexual abuse (Rodgers, Lang, Twamley, & Stein, 2003), and high anxiety during pregnancy (Field et al., 2003). Mothers who had elevated prenatal depressive symptoms have neonates at risk for neurobehavioral dysregulation reflected by less positive affect, lower vagal tone, and elevated cortisol (Field et al., 2006).

Currently, the American College of Obstetrics and Gynecology does not recommend universal screening of pregnant or postpartum women for depression (ACOG, 2010). Without an objective measure to screen for prenatal depressive symptoms, at risk women are not adequately identified. Identifying a biologic marker for prenatal depressive symptoms would aid in early detection, treatment, and decreasing negative sequelae. The purpose of this study was to determine if oxytocin was a biological marker for risk for prenatal depressive symptoms in women.

Oxytocin functions as a neurotransmitter and a blood born hormone in the central and peripheral nervous system (Larsen, Kronenberg, Melmed, & Polonsky, 2003; Speroff & Fitz, 2005). Oxytocin has been referred to as the hormone of "calm, love, and healing" (Uvnas-Moberg, 2003). Oxytocin is mainly synthesized in two regions of the hypothalamus for secretion in the brain and is secreted from the posterior pituitary gland into peripheral circulation (Gimpl & Fahrenholz, 2001). Oxytocin is also synthesized in peripheral tissues such as the uterus, placenta, amnion, corpus luteum, testis, and heart. Oxytocin receptors have been identified in tissues including the uterus, breast, ovary, heart, kidney, thymus, pancreas, and adipocytes (Gimpl & Fahrenholz, 2001). Release of oxytocin from the posterior pituitary and the periphery (uterus, placenta, amnion, corpus luteum, testis, or heart) can be stimulated by social interactions, vaginal stimulation, labor progression, and lactation (Larsen et al., 2003; Speroff & Fitz, 2005; Uvnas-Moberg, 2003). Oxytocin released in the central nervous system does not cross the blood/brain barrier. Central oxytocin release, however, targets neurons that have signaling effects on behavior and on peripheral oxytocin release though the exact mechanism is not fully understood (Larsen et al., 2003; Speroff & Fitz, 2005).

Studies in animal and human models have begun to elucidate the role of oxytocin in behavior. Results of investigations in rats have shown that intracerebroventricular (i.c.v.) administration of oxytocin acts as a primer for maternal behaviors (Galbally,

Lewis, Ijzendoorn, & Permezel, 2011; Pedersen, Ascher, Monroe, & Prange, 1982).

Administration of oxytocin (i.c.v.) to voles, rats, and monkeys led to an increase in social

behaviors including more tactile contact (C. S. Carter, Grippo, Pournajafi-Nazarloo,

Ruscio, & Porges, 2008; Insel et al., 1993). Oxytocin administered into the amygdala

five days after giving birth increased female aggressive behaviors toward intruders, thus

protecting their pups (Ferris et al., 1992). Perfusion of oxytocin into the internal carotid

artery of rats produced an analgesic effect (Kang & Park, 2000). Intranasal

administration of oxytocin has been shown to increase the ability to interpret subtle

social cues and increase trust between two people (Domes, Heinrichs, Michel, Berger, &

Herpertz, 2007; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). In relation to birth,

oxytocin stimulates contractions of uterine smooth muscle aiding in initiation and

progression of labor (Altemus et al., 2001; C. S. Carter et al., 2006). Lactation,

specifically milk ejection, occurs when oxytocin binds to receptors on the myoepithelial

cells of the mammary gland, initiating contractions and expelling milk from the alveoli

into the ducts (Gimpl & Fahrenholz, 2001). Thus, oxytocin appears to have numerous

effects on maternal behavior and the creation of social bonds.

  For this investigation, we were interested in oxytocin as a potential biomarker for

prenatal depressive symptoms due to the putative influence of oxytocin on mothering

behaviors and mother-child interactions. An extreme example of this potential influence

was demonstrated in a study whereby food restriction in oxytocin knockout mice,

resulted in females killing and cannibalizing their pups (Ragnauth et al., 2005). These

findings suggest that in the absence of oxytocin in conjunction with high stress, female

mice failed to exhibit mothering behaviors. In addition, low oxytocin has been linked with

altered patterns of mother-infant interactions, such as less touch (Feldman et al., 2012).

High levels of oxytocin and low levels of cortisol were found to be associated with

greater mother-newborn interactions such as gaze, vocalization, positive affect, and

touch (Feldman, Weller, Zagoory-Sharon, & Levine, 2007b; Levine, Zagoory-Sharon, Feldman, & Weller, 2007). Low oxytocin levels have been identified as a predictor of *postpartum* depressive symptoms (Skrundz, Bolten, Nast, Hellhammer, & Meinlschmidt, 2011). Mothers with depressive symptoms exhibit altered maternal behaviors resulting in negative sequelae for infants (Feldman & Eidelman, 2007; Feldman et al., 2009; Murray & Cooper, 1997; Stein, Malmberg, Sylva, Barnes, & Leach, 2008; Tu et al., 2007). Due to the relationship of oxytocin with maternal behaviors and mother-child interactions, it is plausible that oxytocin may serve as a biologic marker for women at risk for prenatal depressive symptoms.

The goals of this study were to determine 1) the relationship between prenatal depressive symptoms and oxytocin; 2) the relationships between prenatal depressive symptoms and possible contributing factors such as biological factors, psychological status, health behaviors, and life stress; and 3) the relationships between oxytocin and possible contributing factors such as biological factors, psychological status, health behaviors, and life stress. To guide this research, the Biopsychosocial Model for Prenatal Depressive Symptoms was used (Figure 1) (Lutgendorf & Costanzo, 2003). This model portrays biological factors, psychological status, health behaviors, and life stress influencing oxytocin levels, ultimately resulting in prenatal depressive symptoms. To aid in clarity of this model, the concepts of biological factors, psychological status, health behaviors, and life stress are referred to as contributing factors. The Biopsychosocial Model for Prenatal Depressive Symptoms describes these relationships as bidirectional and continuous. The relationships among contributing factors and prenatal depressive symptoms are mediated by oxytocin allowing for the study of oxytocin as a potential biologic marker for women at risk for prenatal depressive symptoms.

B.   Methods

1.   Design

This pilot study is a secondary analysis of a larger longitudinal protocol entitled *Race-related stressors and preterm birth in African American women* (RO3NR010608, Giurgescu, C.). Data were collected at two time points: 15 - 22 weeks (T1) and 25 - 37 weeks (T2). Demographic data, medical history review, self-administered psychological instruments, and blood samples were collected by the parent study.

2.   Setting/Sample

Women were included in the study if they self-identified as African American, were 18 years of age or older, had a singleton pregnancy, presented between 16 - 22 weeks gestation, were able to read and write English, and were living in Chicago. Women were excluded from the parent study if they had chronic hypertension, pre-gestational diabetes, HIV, autoimmune disorders, or a multiple gestation pregnancy, and if they received steroid treatment such as dexamethasone, betamethasone, or asthma medications. Exclusion criteria were selected because these conditions may alter contributing factors and confound study results.

The secondary data analysis included 57 African American pregnant women aged 18 - 36 years. Data were collected at an outpatient facility. Participants were instructed to maintain their usual behaviors including breastfeeding, sexual activity, smoking, or drug use immediately prior to data collection. Sample collection occurred to control for the circadian rhythm of other biologic markers collected in the parent study (Kudielka, Gierens, Hellhammer, Wust, & Schlotz, 2012).

3.   Measures

    a.   Contributing factors

Contributing factors were defined as variables that may be related to prenatal depressive symptoms or oxytocin levels. Contributing factors include biological factors (gravida, maternal age, infant gestational age at birth, infant birth weight, genitourinary infections during pregnancy, current obstetric (OB) history, past OB history, and medical history), psychological status (anxiety), health behaviors (body mass index (BMI), substance use, and education), and life stress (family support, employment, and annual household income).

    i.   Biological factors

Biological factors included gravida, maternal age, infant gestational age at birth, infant birth weight, genitourinary infections during pregnancy, current obstetric (OB) history, past OB history, and medical history. Maternal and infant biological factors were obtained through pregnancy and birth medical records.

    ii.   Psychological status

Psychological status was assessed through a woman's current state anxiety. State anxiety was measured using the state portion of the self-administered State-Trait Anxiety Inventory (STAI) (Kendall, Finch, Auerbach, Hooke, & Mikulka, 1976; Ramanaiah, Franzen, & Schill, 1983; Spielberger, Auerbach, & Wadsworth, 1970). The state subscale of the STAI consisted of 20 items rated on a 4-point Likert scale and included the mothers feeling happy, calm, comfortable, jittery, upset, and confused. Previously reported Cronbach's alpha were 0.85 to 0.95 (Catlett, Miles, & Holditch-Davis, 1994). This study had a Cronbach's alpha of 0.91. Although there is no cutoff, higher scores on the STAI is associated with higher anxiety (Spielberger, 1983).

iii.   Health behaviors

Health behaviors included body mass index (BMI), substance use (smoking and recreational drug use), and education. Body mass index was obtained from pregnancy medical records, while substance use and education were obtained through participant self-administered questions.

iv.   Life stress

Life stress was measured by family support (maternal family involvement, baby's father involvement, and baby's father's family involvement), employment, and annual household income. Family support was assessed through self-administered questions using a 5-point Likert scale ranging from "not involved at all" to "involved a lot". Asking if the baby's father lived with the participant further assessed his involvement. Employment was obtained through a participant self-administered question. Household income was assessed on a self-administered 4-point scale ranging from "less than $10,000 per year" to "greater than $31,000 per year".

b.   Oxytocin

To measure oxytocin level, blood was collected from participants at the previously described time points by the parent study. Blood was centrifuged to obtain a plasma sample, which was divided into aliquots, and frozen for batch analysis. Oxytocin assays were conducted using Assay Designs 96 plate commercial oxytocin ELISA kit. Oxytocin detection levels reported by Assay Designs are 15.6 pg/ml to 1000 pg/ml with sensitivity as low as 11.7 pg/ml. These kits report an intra-assay variance ranging from 8.7% - 12.4% and inter-assay variance ranging from 5.2% - 14.5% (AssayDesigns, 2006). Samples were diluted in the assay buffer (ratio of 1:2) and treated according to directions of the kit. All samples were measured in duplicate. Reliable values of oxytocin were considered if coefficient of variance between duplicates was less than 30%.

c.   <u>Prenatal Depressive Symptoms</u>

Major Depressive Disorder was defined by the DSM-4 as a Major

Depressive Episode not superimposed on another mental disorder and without the

occurrence of mania (APA, 2000). A Major Depressive Episode is defined as five or

more depressive symptoms present in a two week period, most occurring nearly every

day, and causing an individual impairment with social, occupational, or daily functions

(APA, 2000). Prenatal depressive symptoms were measured using the Center for

Epidemiologic Studies Depression Scale (CESD). The CESD consists of 20 depressive

symptoms rated on a 4-point Likert scale. Scores range from 0 - 60 with a cut-off of

greater than 16 identifying elevated depressive symptoms (Radloff, 1977). The CESD

was not developed to assess pregnant or postpartum women, yet it is widely accepted

and used clinically for assessment of Major Depressive Disorder in the general

population (Chung, McCollum, Elo, Lee, & Culhane, 2004; Minkovitz et al., 2005;

Radloff, 1977). In *postpartum* women, the CESD had an internal consistency of 0.82, a

sensitivity of 60%, and a specificity of 92% (Boyd, Le, & Somberg, 2005). In female

African American non-pregnant populations, the CESD is reliable with a Cronbach's

alpha of 0.85 and Spearman-Brown rho of 0.87 (Roberts, 1980). Our study had a

Cronbach's alpha of 0.84 for the CESD.

4.   <u>Procedures</u>

The University of Illinois at Chicago Institutional Review Board approved

the research protocol to conduct oxytocin assays using previously collected blood

samples. Fifty-seven African American pregnant participants had completed the parent

study and their data were available for secondary analysis. All data and blood samples

were de-identified prior to analysis. Blood samples were thawed and oxytocin was

assayed as described above.

5.   Data Analysis

Descriptive statistics were conducted to determine frequencies, means, and ranges for all variables. The following categorical variables had fewer than two participants in each group: substance use, genitourinary infections during pregnancy, past OB history, current OB complications, and past medical history. Dimension reduction was attempted using an extraction method, but was unsuccessful and categories in these variables could not be combined. ANOVA testing was not computed with these variables, though they were included in the regression models discussed below. All analyses were conducted using two-tailed tests when applicable and the level of significance was α = 0.05.

After descriptive statistics were conducted, oxytocin at T1 and T2 were compared using a paired sample *t*-test. The change in oxytocin values from T1 to T2 was computed to help standardize the wide range of possible values. Finally oxytocin values were divided into tertiles (low, average, high) roughly based on oxytocin means.

Prenatal depressive symptoms were included in the analysis as total CESD score and dichotomized for those at risk (CESD > 16) or not at risk. CESD scores at T1 and T2 were compared using a paired samples *t*-test.

To determine the relationship between prenatal depressive symptoms and oxytocin (Aim 1), Pearson's correlations were computed with raw data. After prenatal depressive symptoms were dichotomized, a *t*-test was conducted. To examine the tertiles of oxytocin, an ANOVA was computed with Tukey post-hoc testing.

The relationships between prenatal depressive symptoms and contributing factors (Aim 2) were analyzed as follows. To determine the relationship between prenatal depressive symptoms and gravida, maternal age, infant gestational age at birth, infant birth weight, anxiety, and BMI, Pearson's correlations were computed. To determine the relationships between prenatal depressive symptoms and infant gender or

employment, *t*-tests were computed. To determine the relationship between prenatal depressive symptoms and substance use, education, annual household income, family support (maternal family involvement, baby's father involvement, and baby's father's family involvement), ANOVAs were conducted followed by Tukey post-hoc testing. To further control for contributing factors, a linear regression model was conducted. Analysis continued with an automatic linear regression model using a forward stepwise method. An automatic linear regression model was chosen due to the large number of variables with large variance and the small sample size. It is an initial linear regression that can maximize the results to exhibit the potential relationships mathematically by trimming outliers, replacing missing values, and merging variable categories. The cons of this methodology are that the exact manipulation of the data is performed by the computer and not specified *a priori*.

Finally a classification and regression tree (CART) analysis was performed to further explain how variables attributed to individual participants increased CESD scores. This analysis was conducted separately from the linear regression. The CART analysis was useful for prenatal depressive symptoms because it provided insight as to why some women have greater depressive symptoms.

The relationships between oxytocin values, the change in oxytocin, and contributing factors (Aim 3) were initially evaluated in the same manner as described above for Aim 2. In addition to these analyses, a second classification and regression tree (CART) analysis was performed to explain large changes of oxytocin data from T1 to T2. Finally, oxytocin tertiles were examined with infant gestational age at birth, infant birth weight, and BMI using ANOVA statistics and Tukey post-hoc testing.

C.   Results

     1.   Contributing factors

The sample included 57 African American pregnant women (14 primigravidas, 43 multigravidas) aged 18 - 36 years whose infants were born between 25 - 41 weeks gestation and weighed 400 grams – 4556 grams (Table 1). State anxiety, as measured by the STAI, had a mean at T1 of 34.6 and a mean at T2 of 32.7 (Table 2). A majority of women in this sample were either overweight (38.6%) or obese (29.5%) and without a college degree (86.1%) (Table 3). A large percentage of women (84.9%; 45 participants) had an annual income less than $31,000. Women also had family support as evidenced by maternal family involvement (68.4%), the baby's father's involvement (70%), and the baby's father's family involvement (52.6%) (Table 4).

     2.   Oxytocin

Oxytocin values (Table 5) at T1 ranged from 170 - 2056 pg/ml and at T2 from 194-1794 pg/ml. Mean oxytocin values at T1 were 503.7 pg/ml ($\pm$ 284.2) and at T2 were 529.7 pg/ml ($\pm$ 300.7). One sample was outside the upper limit of detection (1000 pg/ml) by 28 pg/ml (0.028%). Due to the close proximity to the level of detection and the importance of outliers in understanding oxytocin, this sample was kept in the analysis. Five samples had a within sample coefficient of variance greater than 30% and all were included in the analyses. Three of these samples were in the low oxytocin tertile, and the variance between duplicates would not change their categorical classification. Additionally, one sample was categorized in the average oxytocin tertile. The final sample with a variance greater than 30% was categorized in the low oxytocin tertile and was from a participant who had virtually no change in oxytocin values (less than 45 pg/ml) from T1 to T2 scoring less than 5 on the CESD.

No statistical difference in plasma oxytocin values between T1 and T2 were identified when using a paired sample t-test (t = 0.065, df = 42, p = 0.949). The

distribution of oxytocin approximated a bell-shaped curve but had a slight skew to the right. The change in oxytocin from T1 to T2 was computed to standardize oxytocin scores. Fifty-six percent (*n* = 26) of participants had a change in oxytocin less than 100 pg/ml. Twenty-four percent (*n* = 11) of participants had a change in oxytocin between 100 pg/ml – 200 pg/ml. Finally, 19% (*n* = 9) of participants had a change in oxytocin greater than 200 pg/ml. Plasma oxytocin concentrations were divided into tertiles roughly based on oxytocin means values at T1 (503.7 pg/ml) and T2 (529.7 pg/ml). The low tertile included oxytocin values less than 400 pg/ml, the average tertile included oxytocin values between 400 pg/ml - 700 pg/ml, and the high tertile included oxytocin values greater than 700 pg/ml.

       3.   <u>Prenatal depressive symptoms</u>

       CESD values at T1 (*n* = 53) ranged from 0 - 33 with 35.1% scoring above the cutoff for elevated depressive symptoms. At T2 (*n* = 47) the CESD values ranged from 0 – 36 with 22.8% of participants scoring above the cutoff. No statistical difference between T1 and T2 was identified when using a paired sample *t*-test (*t* = -0.88, *df* = 39, *p* = 0.931). The distribution of CESD scores approximated a bell-shaped curve, confirming a normal distribution.

       4.   <u>Relationship between depressive symptoms and oxytocin</u>

       Oxytocin values were not related to CESD scores at T1 or at T2.   When CESD scores were dichotomized, no relationship between oxytocin and CESD scores were identified for either T1 or T2. Oxytocin data was divided into tertiles (less than 400, 400-700, > 700). Women in the low oxytocin tertile had a greater number of depressive symptoms (*F* = 3.265, *df* = 2, 47, *p* = 0.047) compared to women in the high oxytocin tertile (Figure 2).

5.   <u>Relationships between depressive symptoms and contributing factors</u>

Women with a greater number of previous pregnancies had higher CESD scores at T1 (r = 0.319, n = 53, p = .02). Women with higher STAI scores had higher CESD scores at T1 (r = 0.716, n = 47, p = 0.001) and T2 (r = 0.762, n = 41, p = 0.001). Women who reported that the baby's father was not involved had higher CESD scores at T1 (F = 2.676, df = 4, 48, p = 0.043) compared to those who reported more father involvement. A similar trend was identified at T2. Medical history (including prior history of mental health diagnosis), past or current OB history, genitourinary infections during this pregnancy, education, maternal age, gestational age at delivery, and BMI were not related to CESD scores.

The initial linear regression model did not yield significant results. An automatic linear regression was used which automatically trims for outliers, replaces missing values, and merges variable categories to maximize the model. The following variables were identified as related to CESD scores: smoking, anxiety, maternal family involvement, father of the baby involvement, current OB history, maternal medical history, infant gestational age at birth, whether the mother changed her home address, and low oxytocin tertile (r = 0.858, n = 53, p = .0001). This linear regression reported 80.3% of model accuracy in predicting CESD scores.

A classification and regression tree (CART) identified the variables related to the highest CESD scores (Figure 3). Women with no involvement from the baby's father were at increased risk for high CESD scores (CESD = 30.6, n = 3). The next group included women who were diagnosed with an OB complication during their pregnancy (CESD 24.6, n = 3). Women with a previous medical condition categorized as neurologic, pulmonary, or hematologic were the third group identified to be at risk for increased CESD scores (CESD = 21, n = 3). Finally, women with low maternal family support were also at risk for elevated CESD scores (CESD = 19.7, n = 28). Elevated

CESD scores were related to women delivering an infant less than 3106 grams (CESD = 16.9, *n* = 12).

6.   Relationships between oxytocin and contributing factors

With the exception of psychological status (anxiety), oxytocin was related to at least one variable in each contributing factor. Women who had more previous pregnancies (*r* = 0.238, *n* = 54, *p* = 0.083) or a higher BMI (*r* = 0.252, *n* = 52, *p* = 0.071) trended to have elevated oxytocin values at T1. A post-hoc power analysis was computed to determine the sample size needed for significant relationships. A sample size of 130 participants would be needed for a power of 0.80. In older women (*r* = -0.297, *n* = 46, *p* = 0.045) and women who worked longer hours per week (*r* = -0.321, *n* = 42, *p* = 0.038) had a decrease in oxytocin values from T1 to T2. Women in the low oxytocin tertile had infants with lower birth weights (*F* = 2.914, *df* = 2, 47, *p* = 0.064, mean infant birth weight = 2769.35 grams) compared to women who were in the average oxytocin tertile (mean infant birth weight = 3223.23 grams). Women in the high oxytocin tertile trended in the same direction (mean birth weight = 3345.57 grams, Figure 4).

A linear regression model was fit for contributing factors that were related to changes in oxytocin from T1 to T2. This model included substance use, gravida, genitourinary infections during pregnancy, medical history, depressive symptoms, and education (*r* = 0.753, *n* = 46, *p* = 0.001). The model had a predictor accuracy of 63.0% in predicting the change in oxytocin.

A second classification and regression tree (CART) explained variables that were related to positive or negative changes in oxytocin from T1 to T2 (Figure 5). The CART analysis included seven nodes and allowed for further explanation of participants with the greatest positive or negative change in oxytocin. Maternal medical history and recreational drug use were identified as risk factors for the greatest increase in oxytocin.

One participant had multiple medical diagnoses (asthma, anemia, hypothyroid, and psychological illness) and an increase in oxytocin of 798 pg/ml. Oxytocin increased in two participants who reported prior or current recreational drug use (mean change in oxytocin = 458 pg/ml). An opposing finding was with women who currently or previously smoked (*n* = 6). These women had a mean decrease in oxytocin of 182 pg/ml. Though when women used drugs and smoked they had no change in oxytocin and were categorized similarly to those that have never smoked or used recreational drugs (mean change in oxytocin = 34.3 pg/ml, *n* = 38).

Women with a previous obstetrical history (cesarean section or group B beta strep) and no genitourinary infections during the current pregnancy had a decrease in oxytocin (mean change in oxytocin = 400 pg/ml, *n* = 2). Though women with a previous obstetric complications and a genitourinary infection had almost no change in oxytocin (mean change in oxytocin = -72 pg/ml, *n* = 4). Increased maternal age greater than 35.5 was associated with a decrease in oxytocin from T1 to T2 (mean change in oxytocin = -604 pg/ml, *n* = 1). Many variables effected the change in oxytocin, some with opposing relationships as described.

D.   Discussion

In the general population, approximately 20% of pregnant women (3 - 41 weeks) were identified as at risk for elevated prenatal depressive symptoms (Marcus et al., 2003). In this sample of urban primarily low-income pregnant African American women, 33% - 37% reported elevated prenatal depressive symptoms. These findings are consistent with other reports finding African American (Holditch-Davis et al., 2009; Tandon, Cluxton-Keller, Leis, Le, & Perry, 2012) and low income mothers (Chaudron et al., 2010; Segre, O'Hara, Arndt, & Stuart, 2007) are at increased risk of elevated perinatal depressive symptoms. Anxiety and depression are often comorbid conditions

(Kinsella & Monk, 2009). In this study, prenatal depressive symptoms were related to anxiety in the second and third trimester.

Anxiety was measured by the STAI state scale, which does not have a cutoff value to determine high or low anxiety levels. In this sample, anxiety levels were lower than previous reports of women with fibromyalgia (Menzies, Lyon, Elswick, Montpetit, & McCain, 2011) or women in the military (Spielberger, 1983). However, in this study, anxiety levels were similar to previous reports of Caucasian primigravida pregnant women (Aktan, 2010), working women (Spielberger, 1983), and women with chronic renal failure (Theofilou, 2011). We conclude that anxiety level of this sample was appropriate when compared to other groups of women. These pregnant women had anxiety, but not above or below what would be expected.

Both prenatal anxiety and prenatal depressive symptoms have an inverse relationship with social support (Aktan, 2012; Webster et al., 2000). Specifically, the social support of the baby's father is a protective factor for elevated postpartum depressive symptoms (Fagan & Lee, 2010; Mezulis, Hyde, & Clark, 2004; Smith & Howard, 2008). Accordingly, in this sample, prenatal depressive symptoms were higher in women with lower social support.

The automatic linear model identified many relationships between contributing factors and prenatal depressive symptoms, though the quality of this statistical test is difficult to interpret. This type of regression uses mathematical manipulations to create the best mathematical model. The model selection was based on the lowest AIC using a forward stepwise method. The problem with this methodology is if only poor models are available choices, then the best of the poor models would be selected and this is unbeknownst in the statistical reporting, as AIC is a relative number. The results of this model can be used with pilot data to guide future research and make hypothesis. The results cannot be used to make inferences regarding potential relationships.

Several contributing factors previously linked to depressive symptoms, were not identified in this study (Bolton, Hughes, Turton, & Sedgwick, 1998; A. S. Carter, Baker, & Brownell, 2000; Koleva, Stuart, O'Hara, & Bowman-Reif, 2011). Previous research linked smoking to increased risk of depressive symptoms (Boden, Fergusson, & Horwood, 2010) and the comorbidity of recreational drug use and mood disorders (Compton, Thomas, Stinson, & Grant, 2007). These results were not confirmed in the current study, possibly due to the small sample size, the population studied, or the time of pregnancy in which data was collected. Due to the continuous interactions of contributing factors on biological responses, measuring a neuroendocrine mechanism, such as oxytocin, may be a more reliable measure and aid in identification of women at risk.

1.   Change in oxytocin

The CART analysis provided a unique examination of the potential relationships between contributing factors and the change in oxytocin from the second to third trimester. An increase in oxytocin was identified in mothers who had combinations of medical problems or those who had genitourinary infections. These findings have been previously supported in the literature as oxytocin is involved in the inflammatory response (promotes insulin and glucagon secretion) (Gimpl & Fahrenholz, 2001; Pittman, 2011). In the current study, oxytocin also increased in women who used recreational drugs prior to and during their pregnancies. Previous research has identified oxytocin as inhibiting recreational drug use and dependence (McGregor & Bowen, 2011; Sarnyai & Kovacs, 1994). This suggests that oxytocin release is increased in recreational drug use. In this study, oxytocin decreased in women who were smokers *prior* to pregnancy. Based on the literature oxytocin increased in response to smoking (Chiodera et al., 1993), however no evidence exists regarding the longitudinal effects of smoking cessation on oxytocin release.

Women over the age of 35 and those with a past obstetric complication had a decrease in oxytocin. Neither of these findings has been previously studied, though in male rats oxytocin biosynthesis decreased from youth to maturity (Ciosek & Izdebska, 2009). Future research on contributing factors and their potential relationship to oxytocin is warranted and may be accomplished through categorical grouping of oxytocin levels.

  2.   <u>Oxytocin Tertiles</u>

   The wide range of values of oxytocin in this report was consistent with previous research of third trimester women (Feldman, Weller, Zagoory-Sharon, & Levine, 2007a). However, in this sample, *mean* oxytocin values were higher than other reports of second and third trimester levels (303 pg/ml and 263 pg/ml respectively) (Levine et al., 2007). The trend of oxytocin levels in pregnancy has conflicting results (Dawood, Ylikorkala, Trivedi, & Fuchs, 1979; Kuwabara, Takeda, Mizuno, & Sakamoto, 1987; Leake, Weitzman, Glatz, & Fisher, 1981; Levine et al., 2007). Some researchers identified an increase in oxytocin levels through the 39th week of gestation (Dawood et al., 1979; Kuwabara et al., 1987). In contrast to other previous studies in which no difference in oxytocin values were identified between pregnant and non-pregnant populations (Leake et al., 1981). In this sample, we divided oxytocin into tertiles to properly identify low, average, or high values. Dividing oxytocin into tertiles was a useful statistical strategy because of the wide range of values and importance of extremes. By focusing on oxytocin tertiles and their relationships with postpartum depressive symptoms and contributing factors, the maximum number of potential relationships was identified.

   For example, this is the first study to identify an inverse relationship between prenatal oxytocin levels and elevated prenatal depressive symptoms. Women in the low oxytocin tertile had more depressive symptoms, while women in the high oxytocin tertile had fewer depressive symptoms. Prior research identified lower prenatal oxytocin

values as a risk factor for postpartum depressive symptoms at 2 weeks postpartum (Skrundz et al., 2011). Increased prenatal oxytocin values were related to positive postpartum maternal behaviors such as gaze, affect, touch, and vocalization during the first month postpartum (Feldman et al., 2007a). Increased prenatal oxytocin from first to third trimester has been associated with greater mother-infant attachment scores compared to women with stable or decreasing oxytocin (Levine et al., 2007). Postpartum oxytocin levels have been associated with positive affectionate parenting including vocalization, positive affect, and touch (Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010). In a non-pregnant population, decreased oxytocin has been identified in individuals with increased depressive symptoms (Ozsoy, Esel, & Kula, 2009; Scantamburlo et al., 2007). Further research on oxytocin is warranted to identify the biological process behind these findings.

Of interest was the incidental finding of a relationship between oxytocin tertile and infant birth weight. When compared to mothers of the moderate and high oxytocin tertiles, mothers in the low oxytocin tertile delivered infants with lower birth weights. Although the infant birth weight was statistically lower, it did not reach the defined low birth weight of 2500 grams. Contrary to our results, in pregnant rats given exogenous oxytocin during late gestation, rat pups were born 5% - 7% smaller than those not treated with oxytocin (Boer, 1993). To our knowledge, this incidental finding has not been previously studied in humans and requires more exploration to identify the mechanism and relationship between oxytocin and other biological processes effecting infant birth weight.

Study limitations include small sample size, limited variables, blood collection methods, and inclusion of only African American women. The sample size of 57 women did not allow for the power needed to perform all relevant post hoc analyses. For example, the variables including substance use, genitourinary infections during

pregnancy, past OB history, current OB complications, and past medical history had

fewer than 2 participants in each category. After dimension reduction was unsuccessful,

the analyses of these variables were limited because ANOVA testing with post-hoc

statistics were not feasible. With an increase in sample size, the likelihood that each

category would have greater than five participants would allow for further analyses and

potential identification of significant relationships. One limitation of secondary analyses

includes limited variable selection. Variables of interest that were not measured in the

parent study include more extensive psychiatric diagnostic measures, e.g. posttraumatic

stress. Elevated prenatal depressive symptoms have been identified as a risk factor for

elevated postpartum posttraumatic stress symptoms (Soderquist, Wijma, Thorbert, &

Wijma, 2009). Postpartum posttraumatic stress and postpartum depressive symptoms

are known to have a comorbid relationship within the first year postpartum (White,

Matthey, Boyd, & Barnett, 2006). A second limitation of secondary analyses included

the determination of ideal blood sampling methods for oxytocin. Methods used in

oxytocin collection include immediately placing the samples on ice, using pretreated

ethylene diamine tetraacetic acid (EDTA) test tubes, and inquiring about participant

breastfeeding regimens. These methodological issues may have affected oxytocin

results. Finally, these results have low generalizability to other populations due to the

homogenous sampling.

Future research on prenatal depressive symptoms and oxytocin is warranted and

should include prenatal and postpartum measurements of depressive symptoms and

oxytocin with a larger sample size. Additional variables such as psychiatric diagnostic

measures, additional indicators of family support, and mothering behaviors may provide

insight on relationships with oxytocin and prenatal or postpartum depressive symptoms.

The discovery of biologic markers for the identification of women at risk for prenatal

depressive symptoms would assist with more women receiving treatment and decreasing negative outcomes for new mothers and infants.

The findings of this study have clinical implications. A large number of participants were identified as having elevated prenatal depressive symptoms. Screening all pregnant women for prenatal depressive symptoms and obtaining oxytocin levels may allow for early detection and treatment of women at risk. Previous evidence suggests that mood disorders affect mothers and their infants (Feeley et al., 2011; Minkovitz et al., 2005; Murray & Cooper, 1997). Improving maternal and neonatal health should be a priority for obstetric and pediatric primary care providers as well as labor, delivery, and neonatal hospital based providers. Screening mothers with validated screening instruments and assessing oxytocin levels during pregnancy will better identify women at risk for depressive symptoms, aid in the number of women who receive treatment, and therefore improve outcomes. Health professionals should be educated about the functions of oxytocin in the body and its potential as a biologic marker of depressive symptoms. Identification of new mothers with depressive symptoms is imperative to continue improving maternal health, mother-infant interactions, and infant development (Beck, 2008; Weisman et al., 2010).

E. <u>Tables and Figures</u>

TABLE VI: BIOLOGICAL FACTORS	
Gravida	14 (24.6%) primigravida, 43 (75.4%) multigravida
Pregnancy gestation	T1: 15 - 26 weeks, mean: 19.5 (± 2.5) weeks T2: 25 - 37 weeks, mean: 29.7 (± 3.1) weeks Birth: 25 – 41 weeks, mean: 38.6 (± 2.5) weeks
Age	Range: 18 - 36 years, mean: 23.42 (± 4.8)
Infant birth weight	Range: 400 – 4556 grams, mean: 3104.9 (± 689.7)
Infant gender	24 (45.3%) male, 29 (54.7%) female
Genitourinary infections	20 (37%) none 8 (14.8%) Urinary tract infections, 7 (13%) Sexually transmitted infections, 3 (5.5%) candida, 3 (5.5%) Bacterial vaginosis, 2 (3.7%) Other (trichomonas or PID), 11 (20.4%) with combinations of above
Current OB history	36 (65.5%) none 4 (7.3%) Gestational hypertension, 4 (7.3%) premature labor 1 (1.8%) Gestational diabetes, 1 (1.8%) small for gestational age, 1 (1.8%) large for gestational age, 1 (1.8%) pyelonephritis, 1 (1.8%) scant prenatal care, 1 (1.8%) preeclampsia, 5 (9.1%) with combinations of OB complications listed above or including IUGR, Oligohydramnios, Abruption, or low amniotic fluid index (AFI)
Past OB history	43 (79.6% none) 5 (8.8%) previous cesarean section, 1 (1.8%) invasive GBBS, 5 (8.8%) other complications
Medical history	35 (64.8%) none 5 (9.3%) with pulmonary medical issues, 4 (7%) with hematologic conditions, 2 (3.5%) neurologic/seizures, 4 (7%) psychological, 1 (1.8%) hypothyroid, 3 (5.4%) with combinations of the above

TABLE VII: PSYCHOLOGICAL STATUS		
State Anxiety	Range	Mean (standard deviation)
STAI T1	20-62	34.6 (± 11.4)
STAI T2	20-58	32.7 (± 10.1)

TABLE VIII: HEALTH BEHAVIORS	
BMI	Range: 18-50, mean: 27.69 (± 6.96) 2 (4.5%) underweight, 12 (27.3%) normal weight, 17 (38.6%) overweight, 13 (29.5%) obese
Substance use	<u>Drug use only</u>: 1 (1.9%) prior to pregnancy, 2 (3.8%) during pregnancy <u>Smoking only</u>: 6 (11.5%) prior to pregnancy, 0 during pregnancy <u>Smoking and used drugs</u>: 2 (3.8%) prior to pregnancy, 2 (3.8%) during pregnancy <u>None</u> 39 (75%)
Education	12 (21.1%) did not graduate high school, 14 (24.6%) graduated high school 1 (1.8%) technical or vocational school, 22 (38.6%) some college 2 (3.5%) associate degree, 6 (10.5%) bachelor degree or higher

TABLE IX: LIFE STRESS	
Maternal Family involvement	39 (68. 4%) participant family involved a lot
Paternal Family involvement	30 (52.6%) father of baby's family involved a lot
Father of baby involvement	40 (70%) father involved a lot, 30 (52.6%) live with the baby's father, 8 (14%) married
Employment	33 (57.9%) employed
Annual household income	29 (54.7%) less than $10,000, 16 (30.2%) between $11,000 – 30,000, 8 (15.1%) above $31,000

TABLE X: OXYTOCIN AND PRENATAL DEPRESSIVE SYMPTOMS				
	Range	Mean (std dev)	At Risk *n* (percent)	*n* (percent)
Oxytocin				
Oxytocin T1	170 - 2056	503.7 (± 284.2)	X	54
Tertile Low T1	170 - 400		X	19 (35.2%)
Tertile Average T1	400 - 700		X	28 (51.8%)
Tertile High T1	700 - 2056		X	7 (13%)
			X	
Oxytocin T2	197 - 1794	529.7 (± 300.7)	X	49
Tertile Low T2	197 – 400		X	17 (34.7%)
Tertile Average T2	400 – 700		X	24 (49%)
Tertile High T2	700 - 1794		X	8 (16.3%)
Prenatal Depressive Symptoms				
CESD T1	0 - 33	1313 (± 8.64)	20 (37.7%)	53
CESD T2	0 - 36	12.1 (± 8.96)	19 (33.9%)	47

Figure 5

Biopsychosocial Model for Prenatal Depressive Symptoms

Figure 6

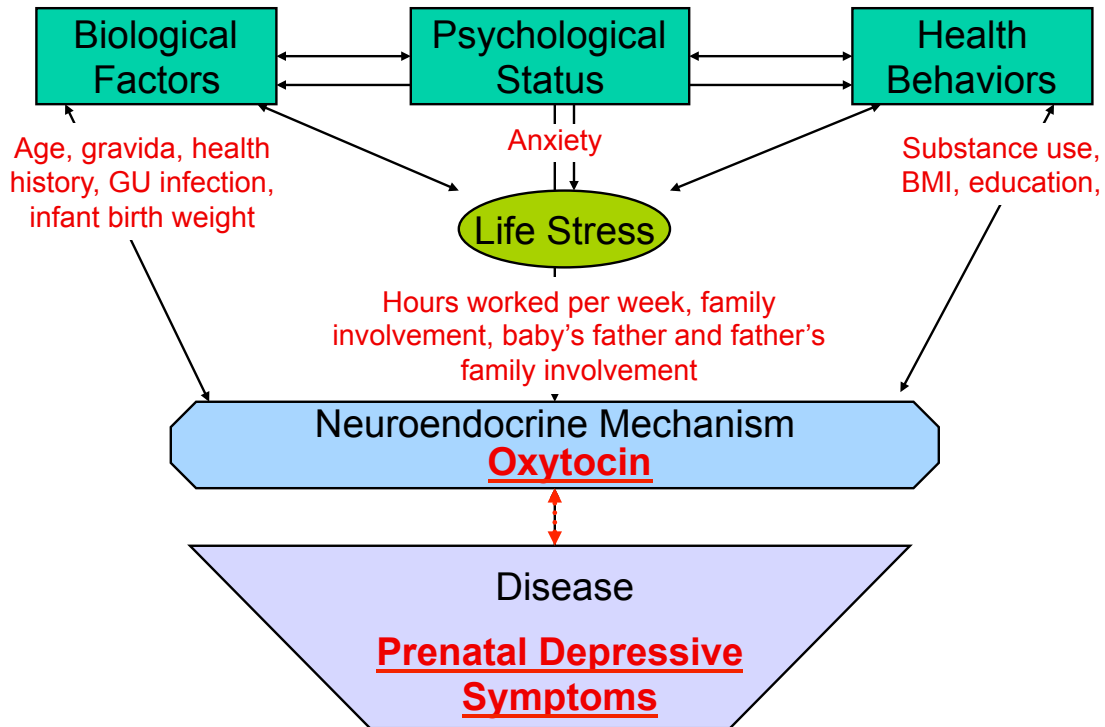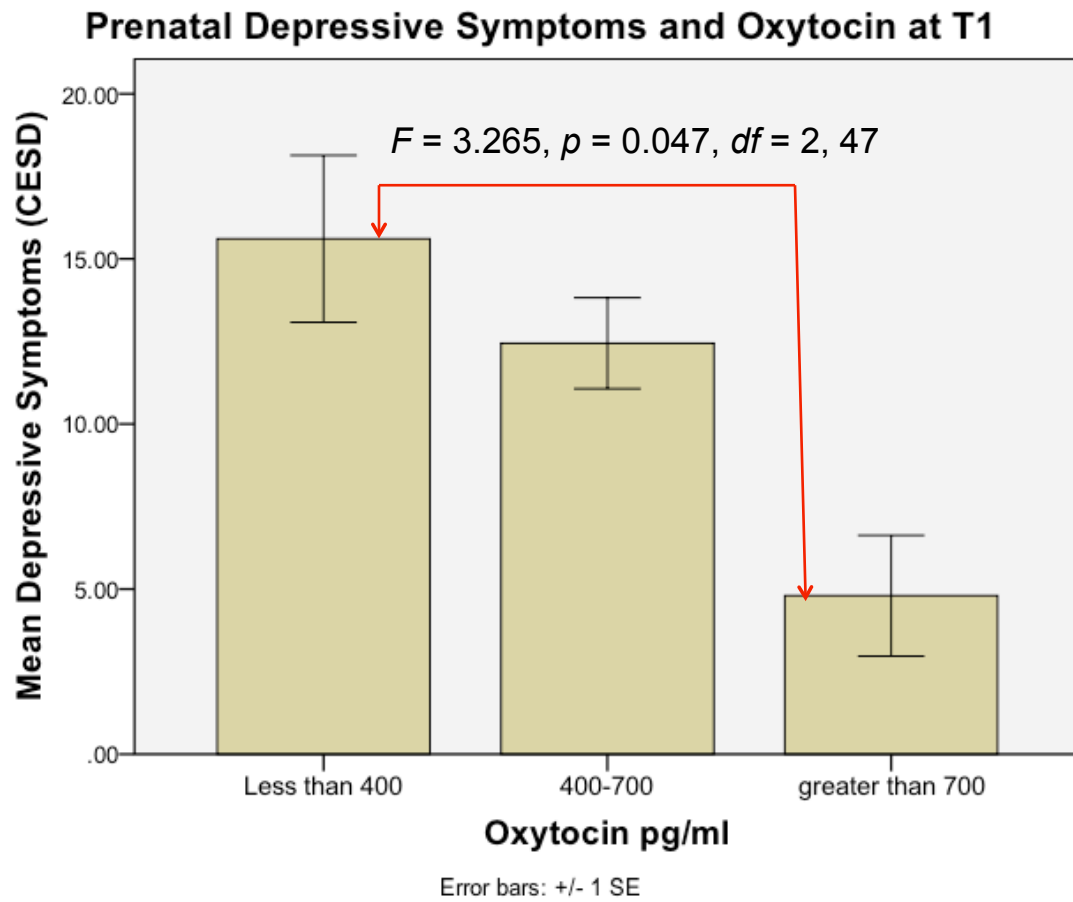Prenatal Depressive Symptoms and Oxytocin at T1

$F = 3.265, p = 0.047, df = 2, 47$

Figure 7: Factors Related to Increased Prenatal Depressive Symptoms

Factor	Prenatal Depressive Symptoms (Sum of CESD)
No father involvement	30.6
Current OB complications	24.6
Medical history	21
Decreased maternal family involvement	19.7
Infant birth weight less than 3106 grams	16.9

Figure 8

Mean Infant Birthweight and Oxytocin at T1

$F = 2.914$, $p = 0.064$, $df = 2, 47$

Figure 9

Factors Related to the Change in oxytocin using CART analysis
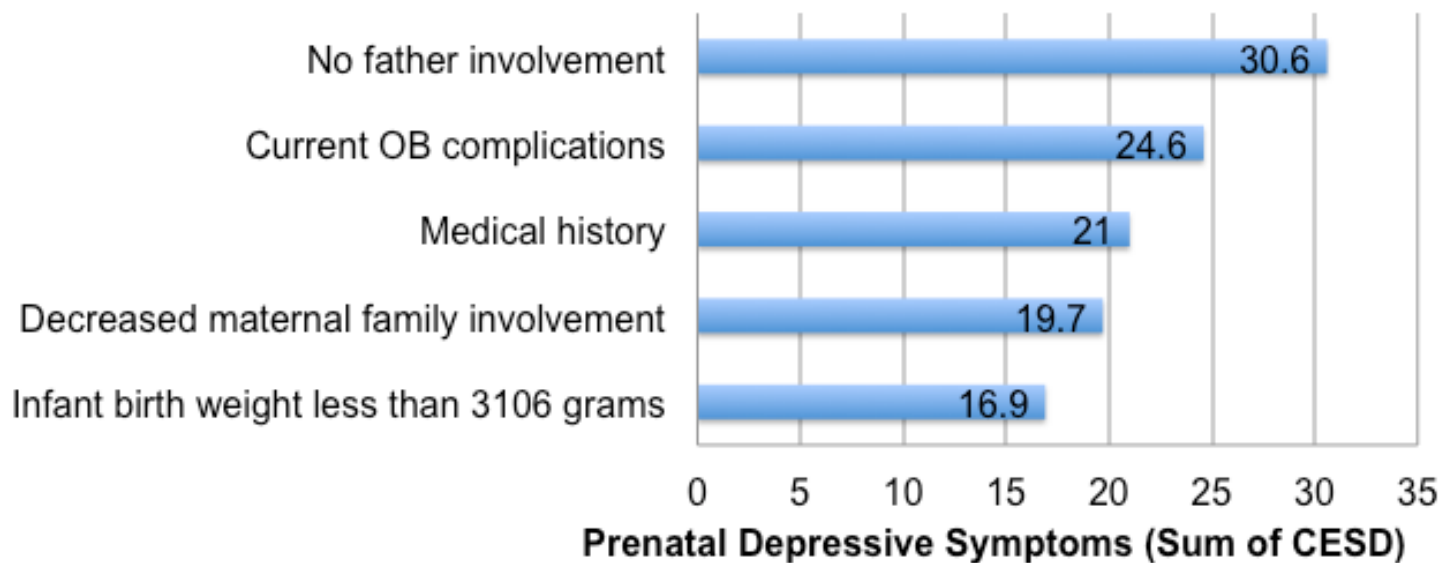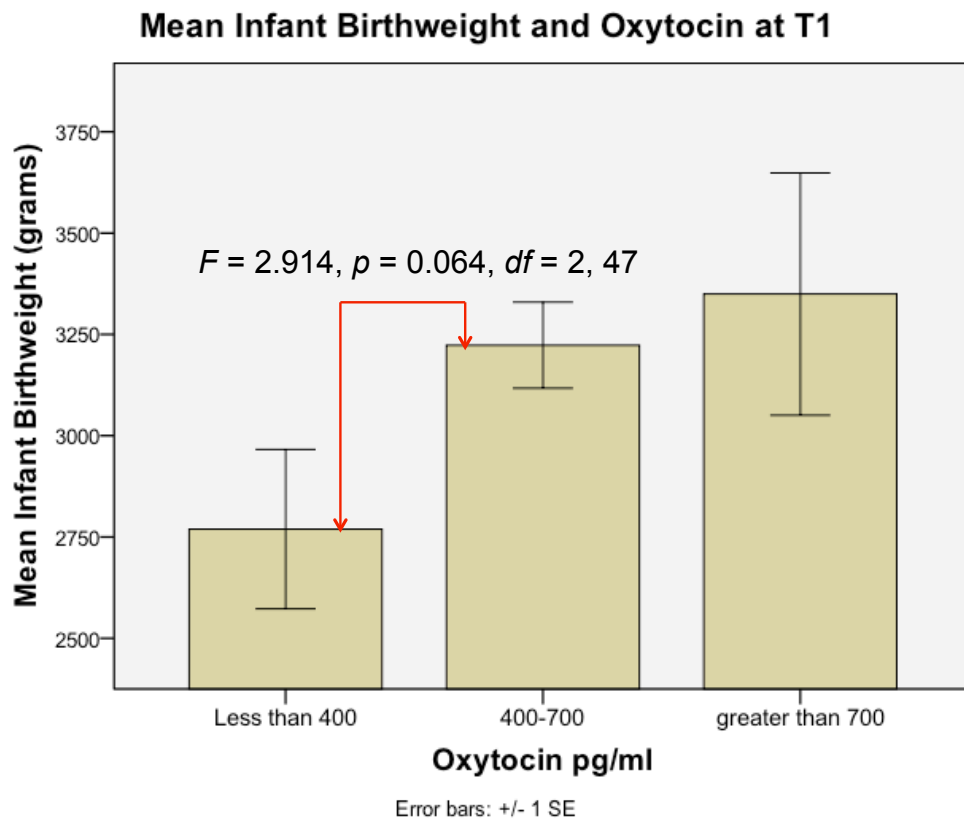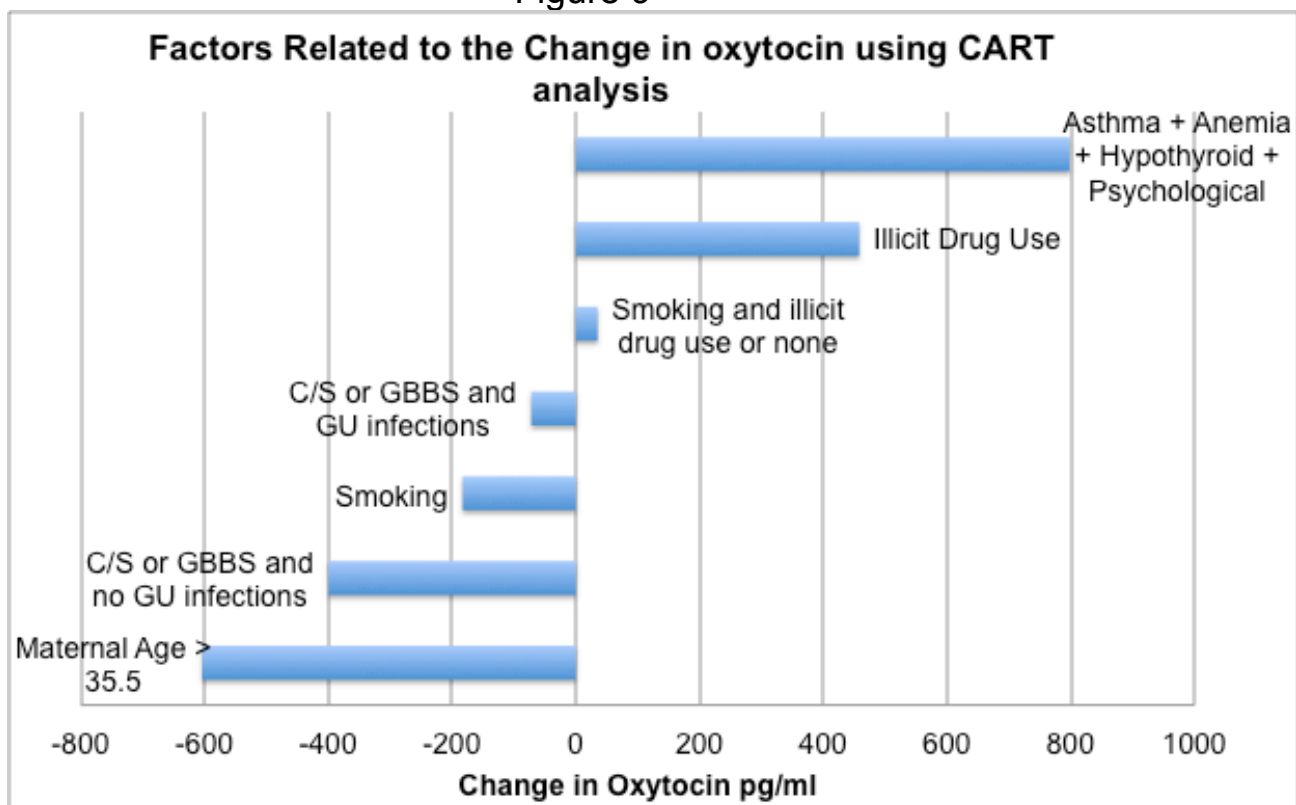
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	Labor and Delivery	
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	Patient Care Technician	2001 - 2002
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