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Depressive Symptoms in the Second Trimester relate to Low Oxytocin Levels in African American Women: A pilot

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Approximately 20% of pregnant women report elevated depressive symptoms.¹ In lowincome, African American women that percentage was doubled (42%).² Women with elevated prenatal depressive symptoms are more likely to have smaller fetuses, premature births, and low birth weight infants.^{3,4} In 2012, 16.5% of African American women experienced a premature birth compared to the national average of 11.5%.⁵ Predictors for prenatal depressive symptoms include young age, single marital status, unemployment, smoking, poor overall health, low education, history of depression,⁶ history of childhood sexual abuse,⁷ lower levels of support,⁸ and elevated levels of anxiety.⁹ Neonates whose mothers have elevated prenatal depressive symptoms are at risk for neurobehavioral dysregulation as reflected by less positive affect, lower vagal tone, and elevated cortisol levels.³ Prenatal depressive symptoms contribute to altered patterns of mother-infant relationships, such as the mother's expressed lack of desire for close contact with her infant, lack of satisfaction with being a mother, hostility, and feelings of resentment toward her infant.¹⁰

The biological mechanisms underlying this health disparity in pregnant African American women are poorly understood. In order to identify women at risk for prenatal depression, providers screen pregnant women using interview techniques or validated screening questionnaires. The American College of Obstetrics and Gynecology, however, does not recommend universal screening of pregnant or postpartum women for depression but recommends screening per the providers' discretion and preference. Understanding the

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biological pathway for prenatal depression in African American women may increase the capacity for identification of women at risk before symptoms are present. Understanding this biological pathway may also enhance opportunities for providing needed treatment of vulnerable mothers. Thus improving infant outcomes. Previous reports have suggested oxytocin may be part of the potential biological pathways involved in perinatal depression. Accordingly, we hypothesized that oxytocin levels may predict perinatal depression.

Oxytocin is a nonapeptide hormone synthesized primarily in the brain, but also in peripheral organs (uterus, placenta, amnion, corpus luteum, testis, and heart). Oxytocin is released in response to various stimuli including social interactions, vaginal stimulation, labor progression, and lactation. Oxytocin release promotes actions relating to the development of social attachments. Oxytocin promotes a desire to touch and be touched, bonding between two people such as husband and wife or mother and child, and initiation of maternal behaviors. Oxytocin have been linked to altered patterns of mother-infant interactions including less touch, whereas high levels of oxytocin have been associated with greater mother-newborn interactions including increased gaze, vocalization, positive affect, and touch. Sinally, low oxytocin levels in pregnancy may be predictive of postpartum depressive symptoms. However, oxytocin has not been explored during pregnancy in an urban African American sample. In a sample of urban African American women, we examined factors potentially associated with prenatal depressive symptoms including plasma oxytocin levels, birth weight/prematurity, demographics, anxiety, support from the infant's father, and maternal health history.

Materials and Method

Design

The data for this secondary analysis were obtained from a larger longitudinal study of pregnant African American women. The larger study was designed to examine stress, pregnancy, and birth outcomes. Data were collected twice during pregnancy (15 - 22 and 25 - 37 weeks). Birth data were obtained from medical records.

Setting

Participants were recruited from a large medical center in Chicago, Illinois. Women were recruited after their standard prenatal care appointment.

Subjects

Subjects included 57 pregnant African American women at a prenatal care appointment between 15 – 22 weeks gestation. Women were invited into the study if they were 18 years of age or older, had a singleton pregnancy, and were able to read and write English. Per the larger longitudinal study, subjects with hypertension, pre-gestational diabetes, human immunodeficiency virus (HIV), autoimmune disorders, a multiple gestation pregnancy, or receiving medications such as dexamethasone, betamethasone, or inhaled steroid were excluded from the study. These characteristics may affect the larger study outcomes of maternal stress and pregnancy.

Measures

Data collected included medical record review for birth outcomes (e.g. gestational age at birth and birth weight), blood samples for plasma oxytocin analysis, and self-reported questionnaires.

Plasma oxytocin was analyzed in duplicate using enzyme-linked immunoassay (ELISA) (Enzo Life Sciences). Oxytocin detection levels were 15.6 pg/ml to 1000 pg/ml.²⁷ The intraassay coefficient of variability was 9.7% to 30% and an inter-assay coefficient of variability was 4.6% to 8.6%.

Self-reported data included a socio-demographic questionnaire in which women indicated their age, marital status, education, household income, and family involvement that included support of the infant's father during pregnancy. Additionally, participants completed previously validated instruments to assess state anxiety and prenatal depressive symptoms,

State anxiety was measured by the State-Trait Anxiety Inventory (STAI). The state subscale of the STAI consists of 20 items (e.g., feeling happy, calm, jittery, upset, confused) rated on a 4-point Likert scale (1 = not at all and 4 = very much so) with scores ranging from 20 - 80. A higher score is associated with higher levels of anxiety. The Cronbach's alpha for this study was 0.91.

Prenatal depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CESD). 29,30 The CESD consists of 20 depressive symptoms (e.g., lonely, sad, restless) rated on a 4-point Likert scale (0 = rarely or none of the time to 3 = most or all of the time) with scores ranging from 0 – 60. A score of 16 or greater indicates clinically elevated depressive symptoms. 31 For this study, the Cronbach's alpha was 0.84.

Procedures

The Institutional Review Board at the University of Illinois at Chicago approved this study. Pregnant African American women between 15 – 22 weeks gestation were invited to participate. After giving informed consent, participants completed the packet of questionnaires in a private room after their prenatal visit. No stimuli were present that may affect oxytocin levels (such as pictures of loved ones, baby toys/dolls, or pregnancy/baby related magazines). On the same day, the participant's blood was drawn into an ethylenediaminetetracetic acid (EDTA) sterile tube (10 ml) and placed on ice. This was completed in the afternoon (1:00 p.m. -5:00 p.m.) for consistency. The samples were transported on ice, centrifuged (1500 × g, 15 minutes), and aliquoted within 3 hours of withdrawal. Once plasma was aliquoted, the samples were stored at -80°C for batch analysis. All assays were conducted according to manufacturer specifications, but samples were not extracted. Participants were given a \$25 gift card for their participation and time. Three participants did not return to the clinic between 25 – 37 weeks and two additional participants delivered prior to the second data collection time. A member of the research team completed a maternal medical record review prenatally and postpartum (for birth data). The participants were not contacted after birth.

Data Analysis

Descriptive statistics were generated to describe sample characteristics. Paired sample *t*-tests were computed to analyze changes in depressive symptoms and oxytocin between the first and second data collection. Independent *t*-tests were computed to examine the relationship between prenatal depressive symptoms and gravida status (primigravida versus multigravida). Spearman's correlation coefficient was computed to examine the relationships among depressive symptoms, raw oxytocin levels, birth weight, gestational age at birth, and anxiety. Analysis of variance was computed to examine depressive symptoms and support of the infant's father during the pregnancy.

Due to the wide range of oxytocin values previously reported in the literature, ¹⁸ after continuous data analysis, raw oxytocin values were categorized as low, normal, and high. These category distinctions were based on previous reports ¹⁷ and graphical cut points. A one-way analysis of variance (ANOVA) was computed to examine the relationships between oxytocin categories and prenatal depressive symptoms, birth weight, and gestational age at birth.

Results

Sample Characteristics

The average age of women in our sample was $23.4~(\mathrm{SD}=4.8)$ years, and ages ranged between 18 and 36 years. Subjects' predominately delivered their infants at term with an average gestational age at birth of $38.6~(\mathrm{SD}=2.5)$ weeks, with ranges from 25-41 weeks. The majority of women were multigravidas (75%). Most subjects did not have a college degree (86%) and had an annual income less than \$30,000 (85%). A majority of women (70%) reported the baby's father was fully involved with the pregnancy. At the first time point subjects reported moderate levels of anxiety $(\mathrm{STAI}=35,\mathrm{SD}=11)$, and 35% had elevated depressive symptoms (score 16 on CESD). No significant differences were found in state anxiety or depressive symptoms between the first and second time point (see Table 1).

The average oxytocin value was 504 pg/ml, SD = 284.2, with a range between 170 and 2056 pg/ml. No significant differences in oxytocin levels were found between the first and second time point. Therefore, we conducted the remaining analysis only with the first data point. Oxytocin data was divided into low (<400 pg/ml), medium (401–700 pg/ml), and high (>701 pg/ml) categories, based on the distribution of the data and corroborated by previous reports on oxytocin. The low category represented the lower 35%, while the high category represented the upper 10%. The mean depressive symptoms in the low, normal, and high oxytocin categories were 15.6, 12.4, and 5.3 respectively (see Table 2).

Factors Associated with Prenatal Depressive Symptoms, Oxytocin and Birth Weights

Depressive symptoms were higher in multigravidas ($t_{(51)} = -2.37$, p = 0.02), women with higher anxiety ($r_{(47)} = 0.71$, p = 0.001), women who delivered their infants at an earlier gestational age ($r_{(51)} = -0.29$, p = 0.04), and those without the support of the infant's father ($F_{(4,48)} = 2.676$, p = 0.04). There was no statistical relationship between depressive

symptoms and birth weight ($r_{(50)} = -0.21$, p = 0.15) or raw oxytocin levels($r_{(51)} = -0.10$, p = 0.53). After depressive symptoms were dichotomized into elevated and non-elevated (CESD score 16), there continued to be no statistical relationship between elevated depressive symptoms and birth weight ($t_{(48)} = 1.4$, p = 0.17), or raw oxytocin levels ($t_{(48)} = 0.60$, p = 0.55). In addition there was no relationship between the group of participants with elevated depressive symptoms (CESD score 16) and oxytocin category (low, medium, or high) ($X^2_{(2, N = 50)} = 3.5$, p = 0.18).

Oxytocin categories (low, medium, or high) and depressive symptoms (CESD scores) were related. Depressive symptoms were higher in women with low levels of oxytocin (n = 17) compared to women with high levels of oxytocin (n = 5) ($F_{(2,47)} = 3.3$, p = 0.05, Fisher's Least Significant Difference (LSD) = 0.015) (see Figure 1).

In addition, women with low levels of oxytocin also tended to be more likely to have infants with lower birth weights compared to women categorized as having medium and high levels of oxytocin ($F_{(2,47)} = 2.9$, p = 0.06, LSD = 0.037, 0.063 respectively); although this difference in birth weights is not clinically significant (see Figure 2). There was no relationship between oxytocin categories (low, medium, or high) and gestational age at birth.

Discussion

In pregnant African American, primarily low-income women, a large percentage (35%) experienced elevated prenatal depressive symptoms. Depressive symptoms were higher in multigravidas, women who reported greater anxiety, and in women without involvement from the baby's father. In addition, women with elevated prenatal depressive symptoms more frequently had low levels of prenatal oxytocin and earlier gestational ages at birth.

The prevalence of elevated prenatal depressive symptoms is consistent with other studies of pregnant African American women 33,34 and low income mothers. 35,36 Previous reports also identified anxiety and depression as comorbid conditions. 37 In addition, we found the mean anxiety levels in our sample (STAI mean = 34) were similar to other reports from low–income, predominately African American pregnant women (STAI mean = 39). 38 Other researchers have found that women with low levels of social support also reported higher levels of prenatal depressive symptoms. 39,40 Specifically, the social support of the infant's father has been identified as a protective factor for elevated postpartum depressive symptoms. $^{41-43}$

The wide range (170 – 2056 pg/ml) of raw oxytocin levels reported in this investigation is consistent with previous studies using a similar methodology. ^{13,44} The range of possible oxytocin values between our sample and other reports are comparable with oxytocin values in some cases exceeding 2000 pg/ml. The mean value of oxytocin from our sample was 504 pg/ml, compared to values of approximately 300 pg/ml, which are typical of other populations using identical measures. ^{13,44} The comparatively high levels of oxytocin measured in this study may reflect physiological coping mechanisms associated with lifestyle in this vulnerable low-income pregnant African American population.

We identified a relationship between low oxytocin category and increased prenatal depressive symptoms. Prior reports have identified lower prenatal oxytocin values as a risk factor for *postpartum* depressive symptoms.²¹ In addition, the literature provides support that higher prenatal oxytocin values are related to positive postpartum maternal behaviors such as gaze, affect, touch, and vocalization during the first month postpartum.¹³ Higher *postpartum* oxytocin levels have been associated with positive affectionate parenting including vocalization, positive affect, and touch.¹⁶ In a non-pregnant population, lower oxytocin has been identified in individuals with greater depressive symptoms.^{19,20}

Women with low prenatal oxytocin levels delivered infants who tended to have lower birth weights when compared to mothers with medium and high oxytocin levels. The mean difference in birth weight was not clinically significant, but it raises the question of the potential relationship between these factors.

Study Limitations

Limitations of this study include 1) small sample size, 2) limited variables, and 3) inclusion of only African American women. The sample size of 57 women included 6 women who had a premature birth. Further analysis with premature birth, prenatal depressive symptoms, and oxytocin were limited based on the small number of premature births. Second, because this study was a secondary analysis of existing data, we were limited by its design and the data collected. For example, longitudinal data from the postpartum period may have provided a more complete understanding of the ways these factors are associated. The third limitation is based on the homogeneity of the sample. The urban, low income, African American women in our sample may have experienced unique life events affecting their oxytocin levels and their self-report of prenatal depressive symptoms. This sample was chosen due to the known increased risk of prenatal depression in African American women, yet this limits the generalizability of these results.

Conclusions

A large percentage of pregnant African American urban women, report elevated prenatal depressive symptoms. There are many factors related to elevated prenatal depressive symptoms and oxytocin may be one of the biological pathways explaining this increased risk. Understanding the biologic pathway of prenatal depressive symptoms may also explain other pregnancy health disparities in African American women such as premature birth. Identifying the biological pathway for depressive symptoms might allow for improved identification and future treatment. Early identification of pregnant women at risk for depressive symptoms may improve known sequelae such as maternal health, mother-infant interactions, and infant development. 45,46

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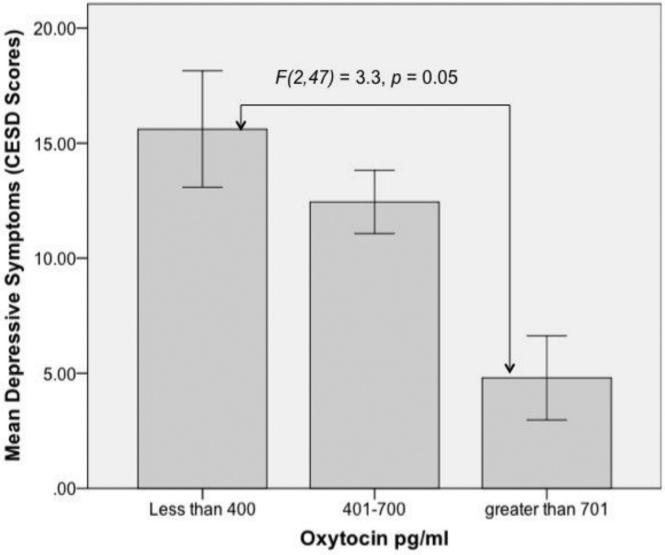
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Prenatal Depressive Symptoms and Oxytocin



Error bars: +/- 1 SE

Figure 1. Prenatal Depressive Symptoms and Oxytocin. Women with low oxytocin levels had more depressive symptoms compared to women with high oxytocin levels. Error bars represent one standard error from the mean. CESD: Center for Epidemiologic Studies Depression scale. Sample size for the groups is as follows: less than 400, n = 18; 401-700, n = 27; greater than 701, n = 5.

Infant Birth Weight and Oxytocin

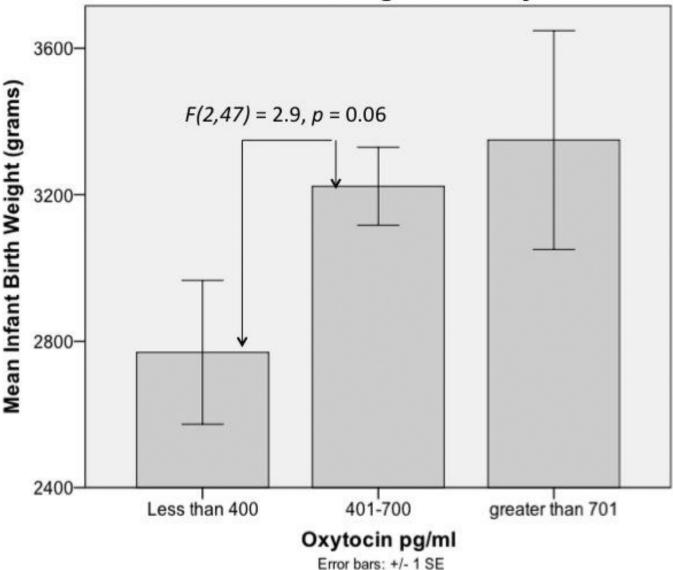


Figure 2. Infant Birth Weight and Oxytocin. The relationship between prenatal oxytocin category and infant birth weight trended toward significance. The relationship between infant birth weight and raw prenatal oxytocin values was not significant. Error bars represent one standard error from the mean. Sample size for the groups is as follows: less than 400, n = 17; 401-700, n = 27; greater than 701, n = 5.

Table 1

Sample Characteristics

	Mean (SD)
Maternal age (years)	23.4 (4.8)
Gestational age (weeks)	
First data point	19.5 (2.5)
Second data point	29.7 (3.1)
Birth	38.6 (2.5)
Infant birth weight (grams)	3105 (690)
Multigravida	75%
Education	
% Less than High School	21%
% High School Graduate	24%
% Some College	44%
% College Graduate	11%
Marital Status	
Single	84%
Married	14%
Separated	2%
Income less than 30,000	79%
Baby's father involvement	
Not involved	11%
Moderately involved	19%
Fully involved	70%
State Anxiety (STAI)	
First data point	34.7 (11)
Second data point	32.8 (10)
Depressive Symptoms (CESD)	
First data point	13 (8.6)
Second data point	12 (9.0)
CESD score 16 or greater	
First data point	35%
Second data point	33%

 $Note.\ STAI = State\ Trait\ Anxiety\ Inventory.\ CESD = Center\ for\ Epidemiology\ Studies - Depressive\ Scale$

Table 2

Mean (SD) of the Oxytocin Values in the total Sample and by the Oxytocin Categories

	Oxytocin (pg/ml)	Depressive symptoms (CESD scores)	Birth Weight (grams)	N
Sample Means	504 (284)	13.1 (8.6)	3105 (690)	50
Categories of Oxytocin				
Low Oxytocin (<400)	304 (70)	15.6 (10.7)	2769 (811)	18
Medium Oxytocin (401–700)	508 (73)	12.4 (7.1)	3223 (542)	27
High Oxytocin (>701)	1030 (475)	5.3 (4.6)	3350 (791)	5