

**Depression, Anxiety, and Stress in Women Misusing Opioids During Pregnancy and
Effects on the Development of Neonatal Opioid Withdrawal Syndrome**

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Samantha Kay Noose

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ABSTRACT

Anxious and depressive disorders are prevalent among women who misuse opioids during pregnancy. Furthermore, these disorders have been linked to the development of neonatal opioid withdrawal syndrome (NOWS) in infants exposed to opioids in-utero. The role of stress in pregnancy among women misusing opioids remains to be understood, however, despite its relevance to anxiety, depression, and substance use. The present study aimed to expand upon current research by comparing symptoms of anxiety, depression, and stress in a sample of women who misused opioids during pregnancy ($n = 53$) and women with high-risk pregnancies for reasons unrelated to drug use (e.g., obesity, heart/blood disease; $n = 37$). This study additionally examined whether depression, anxiety, and stress symptoms during pregnancy predicted whether infants were born with NOWS. Findings revealed significantly higher depression, anxiety, and stress among pregnant women who misused opioids than among pregnant women with high-risk pregnancies unrelated to drug use. Furthermore, results indicated that higher anxious symptoms and lower stress symptoms contributed to a greater likelihood of infants developing NOWS after delivery. Post hoc analyses revealed that stress and anxious symptoms only emerged as significant predictors of NOWS within the group of women who tapered to lower doses of opioids prior to delivery. Conversely, symptoms of depression, anxiety, and stress did not significantly predict NOWS within the group of women who maintained a stable, prescribed dose of opioids throughout pregnancy or within women who completely detoxified from opioids by the time they gave birth, as there was little to no variability within these groups. Clinical implications, future directions, and limitations of the present study are discussed.

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CHAPTER ONE

INTRODUCTION AND BACKGROUND

Opioid misuse during pregnancy has become a rapidly increasing public health issue in the United States, as prevalence rates more than quadrupled between 1999-2014 (Haight, Ko, Tong, Bohm, & Callaghan, 2018). As a result, there is an imperative need to understand the experience of women struggling with opioid misuse in pregnancy in order to inform treatment efforts (American College of Obstetricians and Gynecologists [ACOG], 2017, August). Substantial research has recently demonstrated that anxious and depressive disorders exist in high rates among women who misuse opioids during pregnancy (ACOG, 2017, August). The present study aimed to expand on this research in three ways. First, we assessed anxious and depressive symptoms along a continuum, as opposed to with categorical diagnoses, given the likelihood that not all pregnant women struggling with opioid misuse will have access to the mental health resources needed to provide diagnoses. Second, we compared anxiety and depression in women who misuse opioids in pregnancy with women with high-risk pregnancies for reasons unrelated to drug use, who are also at risk for experiencing such symptoms. Third, we examined similarities and differences in stress symptomatology between these groups. By addressing these gaps, we aimed to identify whether high symptoms of depression, anxiety, and stress were related specifically to the unique challenges of opioid use during pregnancy, or if they may be attributed to having a high-risk pregnancy in general. An increased understanding of the issue may have important implications for effectively treating opioid use in pregnant women, such as informing screening procedures that would aid in identifying women in need of simultaneous mental health care to remain healthy throughout their pregnancies.

Anxiety and depression during pregnancy have been linked to the development of neonatal opioid withdrawal syndrome (NOWS) in infants (Faherty, Matone, Passarella, & Lorch, 2018; Hensley, Sulo, Kozmic, & Parilla, 2018). NOWS, previously termed neonatal abstinence syndrome (NAS), is a unique consequence of opioid exposure during pregnancy (whether prescribed or illicit). NOWS is characterized by dysfunction in an infant's gastrointestinal, autonomic and central nervous systems after birth, and is associated with various health deficits throughout development (ACOG, 2017, August; Conradt, Crowell, & Lester, 2018; Seifer et al., 2004; Towers et al., 2019). Although it has been well-established that opioid use during pregnancy poses significant risk in terms of infants being born with NOWS, a mother's opioid use alone does not guarantee that an infant will be born with this condition. There is unexplained variability in whether or not opioid-exposed infants go on to develop NOWS (Brandt & Finnegan, 2017; Jansson, Velez, & Harrow, 2009; Patrick et al., 2015; Stuart et al., 2018). According to the biopsychosocial theory of illness (Engel, 1977), it is important to consider not only biological and pharmacological factors that contribute to the development of NOWS, but psychological factors, as well. Given that anxiety and depression are prevalent among women who misuse opioids during pregnancy, that stress is often comorbid with anxiety and depression in pregnant women, and that these mental health issues are often associated with adverse birth outcomes (Alder, Fink, Bitzer, Hösli, & Holzgreve, 2007; Schetter & Tanner, 2012), the present study investigated whether symptoms of depression, anxiety, and stress explain some of the variability that exists in whether an infant goes on to develop NOWS.

Anxiety, Depression and Opioid Misuse during Pregnancy

For pregnant women in general in the United States, the prevalence of anxiety disorders is estimated at approximately 12%, major depressive disorder is approximately 5.6%, and dysthymia is approximately 1% (Vesga-Lopez et al., 2008). However, in the last decade, a higher prevalence of anxious and depressive symptoms and disorders in samples of pregnant women struggling with opioid misuse has been highlighted in multiple studies (ACOG, 2017, August; Arnaudo, Andraka-Christou, & Allgood, 2017; Benningfield et al., 2010; Fitzsimons, Tuten, Vaidya, & Jones, 2007). For example, Fitzsimons and colleagues (2007) estimated that in opioid misusing pregnant women (gestation between 8-23 weeks), the prevalence of mood and anxiety disorders was approximately 73%. Additionally, Benningfield and colleagues (2010) found that 32% of their sample of opioid misusing pregnant women met criteria for major depressive disorder (MDD), 31% met criteria for dysthymia, and 40% met criteria for an anxiety disorder. More recently, in a study conducted by Hensley and colleagues (2018), 60.8% of their sample of opioid-dependent women had a diagnosis of an anxious or depressive disorder. Only one study has examined anxious and depressive disorders in pregnant women who misused prescription opioids in comparison to pregnant women who did not engage in prescription opioid misuse (Smith, Costello, & Yonkers, 2015). The findings of this retrospective study indicated that women who misused prescription opioids during their first trimester of pregnancy were more likely to have a comorbid diagnosis of major depressive disorder (16%) or generalized anxiety disorder (18%) than pregnant women who did not misuse prescription opioids (8% and 9%, respectively; Smith et al., 2015).

Taken together, these studies demonstrate consistently high rates of anxious and depressive disorders in samples of pregnant women who use prescribed and/or illicit opioids

throughout their pregnancies. This makes sense, given that women who misuse opioids during pregnancy face a unique set of problems related to their drug use, including their own detoxification or management of their addiction, the social stigma that they face, and the threat of losing custody of their child or facing legal consequences after their infants are born (Borders & Booth, 2007; Corrigan & Nieweglowski, 2018; Howard, 2015). However, no studies have examined self-reported anxious and depressive symptoms, as opposed to disorders, in women struggling with opioid misuse during pregnancy compared to other groups of pregnant women. Thus, the present study sought to examine anxiety and depression across a continuum of self-reported symptoms. This is important for two reasons – 1) examining symptomatology as a continuous variable may contribute to greater power to assess anxiety and depression than would a categorical diagnosis, and 2) it is possible for individuals to experience symptoms of anxiety and depression without having a formal diagnosis, so assessing these constructs more dimensionally would provide a broader perspective on experiences of anxiety and depression in pregnant women misusing opioids.

Anxiety and Depression among Women with High-Risk Pregnancies

An additional gap in the literature is that no studies have compared anxiety and depression in women misusing opioids during pregnancy to other pregnant women with high rates of psychiatric comorbidities, such as women with medically high-risk pregnancies. Thus, the present study introduced a comparison group comprised of women who have high-risk pregnancies for reasons unrelated to drug use. This comparison group was of interest for two reasons: 1) that opioid misuse during pregnancy qualifies that pregnancy as medically high-risk

with unique consequences for the mother and neonate, and 2) research suggests that women with high-risk pregnancies also experience high rates of clinically significant anxiety and depression.

According to a recent review (Rodrigues, Zambaldi, Cantilino, & Sougey, 2016), approximately 22% of pregnant women are considered to have high-risk pregnancies due to a pre-existing or pregnancy-specific medical condition (not including drug misuse) which puts the expecting mother and her fetus at risk for health complications. While ample research has consistently demonstrated more anxious and depressive disorders in women who use opioids during pregnancy, it has also been suggested that women with high-risk pregnancies for reasons unrelated to drug use are at increased risk for experiencing symptoms of anxiety, depression, and other mental health concerns due to the nature of their pregnancies and potential for negative outcomes (Denis, Michaux, & Callahan, 2012; Maloni, Park, Anthony, & Musil, 2005; McCain & Deatricks, 1994; Rodrigues et al., 2016; Thiagayson et al., 2013). Additional research examining differences between women who are experiencing high-risk pregnancies due to opioid use versus for reasons unrelated to drug use would help to distinguish whether anxiety and depression is consistent across groups. This could potentially indicate that high anxiety and depression are characteristic of experiencing a high-risk pregnancy in general, or that they are exacerbated by opioid use. Given that opioid use poses unique consequences for pregnant women in addition to health concerns, such as coping with addiction, social stigma, and potential legal consequences, in the current study, we expected to find that pregnant women who used prescribed and/or illicit opioids would report more anxious and depressive symptoms than mothers who have high-risk pregnancies for reasons unrelated to substance use.

The Role of Stress in High-Risk Pregnancies

Studies find that stress is a prevalent factor among women experiencing medically high-risk pregnancies (Kemp & Hatmaker, 1989; Wang et al., 2019). However, no studies to date have examined maternal stress during pregnancy in a sample of pregnant women misusing opioids. This is surprising, given that stress is often comorbid with anxiety and depression in pregnant women (Alder et al., 2007), including in samples of high-risk pregnant women and women who misuse substances during pregnancy (Chaplin & Sinha, 2013; Rodrigues et al., 2016). This is an important gap to address, given that maternal stress levels during pregnancy are associated with adverse birth outcomes (Alder et al., 2007; Lobel, DeVincent, Kaminer, & Meyer, 2000; Mulder et al., 2002; Schetter & Tanner, 2012). The present study examined differences in stress symptomatology between opioid misusing and non-drug using women with high-risk pregnancies. Because of the unique stressors that women struggling with opioid misuse face during pregnancy, we hypothesized that this group would have the highest levels of stress.

Link Between Anxiety, Depression, Stress, and NOWS

Opioid misuse during pregnancy poses high risk for a variety of birth complications to infants, including low birth weight, preterm birth, and most uniquely, NOWS (ACOG, 2017, August; Brandt & Finnegan, 2017). While studies have also suggested a link between anxiety, depression, stress, and adverse birth outcomes (Alder et al., 2007; Schetter & Tanner, 2012), research has only recently begun to suggest that there is a link between mothers' anxiety and depression when misusing opioids during pregnancy and the presence of NOWS in their infants shortly after birth, which suggests that anxiety and depression may help to explain some of the variability in the development of NOWS. Faherty and colleagues (2018) found that in their

retrospective study of young women on Medicaid and their infants, mothers who gave birth to infants with NOWS were significantly more likely to have a diagnosed depressive or anxiety disorder during the prenatal period than those whose infants were born without these conditions and whose Medicaid records did not include opioid dependence diagnoses or evidence of medication-assisted treatment for opioid use during pregnancy (e.g., methadone, buprenorphine; Faherty et al., 2018). A limitation of this study, however, is that it retrospectively examined whether women had a diagnosis of an anxious or depressive disorder based on International Classification of Disease – Ninth Revision (ICD-9) codes in their Medicaid claims. This may leave out women who are struggling with significant anxious and depressive symptoms, but whom have not received a diagnosis of depression or anxiety. In another study, Hensley and colleagues (2018) found that in a sample of pregnant women who were receiving either methadone or buprenorphine treatment for opioid misuse, those who also had comorbid depression were significantly more likely to give birth to infants who were treated for withdrawal symptoms and who had significantly longer neonatal intensive care unit (NICU) stays than women who did not have depression. However, this study only examined how diagnoses of a depressive disorder or clinically significant depressive symptoms during pregnancy were related to infant withdrawal symptoms as a secondary aim. They did not examine anxiety during pregnancy.

While these studies highlight a relationship between prenatal maternal anxiety and depression in women misusing opioids during pregnancy and infant withdrawal symptoms following birth, additional research is needed to support this link. Again, these studies focus primarily on how diagnoses of depression and anxiety during pregnancy relate to NOWS development in infants. No research thus far has examined how self-reported anxious and

depressive symptoms during pregnancy predict NOWS. Thus, the present study expanded the focus on a broader range of anxious and depressive symptoms that women may be struggling with during pregnancy, and how these symptoms relate to the development of NOWS above and beyond the amount of opioids they were taking at delivery based on their treatment plans.

Additionally, no studies have examined maternal stress during pregnancy in relation to the development of NOWS in infants. Given the comorbidity of stress with anxiety and depression in pregnant women (Alder et al., 2007) and that stress during pregnancy is associated with increased motivation to use drugs (James Bell & Harvey-Dodds, 2008), it is an important factor to investigate that may aid in explaining some of the variability in the development of NOWS. A goal of the current study was to examine maternal self-reported stress symptoms in relation to NOWS after controlling for the status of women's opioid use based on their treatment plan at delivery.

The Present Study

In the present study, we sampled pregnant women who were prescribed and/or who were misusing opioids, as well as a comparison group of women who were experiencing medically high-risk pregnancies for reasons unrelated to drug use (e.g., multiple gestation, morbid obesity, heart disease, blood disease). First, we hypothesized that pregnant women who used opioids (either illicit or prescribed) would report more symptoms of depression, anxiety, and stress compared to high-risk comparisons. Second, we hypothesized that within the group of pregnant women who used opioids (either illicit or prescribed), symptoms of depression, anxiety, and stress during pregnancy would predict the presence of NOWS in their infants after birth above and beyond opioid detoxification status at birth.

CHAPTER TWO

METHODS

Participants

The sample ($N = 90$) consisted of pregnant women who were patients at a high-risk obstetrical clinic during pregnancy. Fifty nine percent of participants ($n = 53$) were referred to the clinic for reasons related to opioid misuse during pregnancy, and they had a urine test that was positive for opioid use within 30 days of participating in this study. The other 41% of mothers ($n = 37$) were referred to the clinic for other reasons associated with high-risk pregnancy, ranging from common high-risk factors (e.g., multiple gestation), to serious medical complications or illnesses (e.g., morbid obesity with Body Mass Index > 50 , cardiovascular, cardiopulmonary, hypercoagulable, or rheumatologic diseases). Nine participants from the original sample ($N = 99$) were excluded from the analyses in the present study due to a) giving birth at a different hospital, meaning that we were unable to access information about their infants following birth ($n = 3$) or b) being referred to the high-risk obstetrical clinic for substance use that did not include opioid use ($n = 6$). In terms of demographics, women in the opioid use group tended to be older and less likely to identify with a minority ethnic background than women in the no opioid use group (See Table 1 in the Appendix). There were no differences in demographic or gestation variables between groups. All women in the present study received Medicaid, indicating low socioeconomic status.

Procedure

Participants were recruited from a high-risk obstetrical clinic. At Time 1, obstetricians approached their patients during a regular visit and invited them to participate in this survey

study if they were interested. Physicians told their patients that participation was completely voluntary, and that they would receive a \$25 Walmart gift card if they chose to participate. Upon indicating her interest in the study, the physician introduced each participant to a research assistant who went over a consent form with her. Upon providing consent, women volunteered to participate in the study and permitted research assistants to access their medical charts for additional information. Each participant then completed a self-report questionnaire regarding her anxious and depressive symptoms. Following women's enrollment in the study, research assistants collected information from their medical charts, including demographics, opioid use (e.g., based on urinalysis results, prescribed medications, physician notes), and gestation (in weeks) at the time of enrollment. After participants gave birth to their infants (Time 2), a physician and an obstetrical resident at the hospital obtained information regarding birth outcomes from participants' medical charts. This information included gestational age of infants at delivery, mother's treatment outcome at the time of delivery (i.e., whether mothers maintained on medication-assisted treatment throughout pregnancy [MAT], chose to gradually taper to lower, prescribed dosages of opioids throughout pregnancy, or achieved complete detoxification from opioids), and whether infants developed NOWS after birth.

Measures

Demographics. At each participant's first visit at the high-risk obstetrical clinic, they filled out a demographic information form, including age, race/ethnicity, employment status, marital status, and medical insurance. See Table 1 in the Appendix.

Gestation. We recorded the number of weeks pregnant that each woman was at the time of enrollment in the study. All participants were in their second or third trimester at the time of

enrollment. There were no significant differences between groups in terms of gestation at the time of enrollment in the study. See Table 1.

Opioid Use. We created a dichotomous variable in order to assign participants to either the “opioid use” group, or the “no opioid use” group. This variable is based on participants’ urine samples taken within 30 days prior to consenting to participate in the study. Specifically, we assigned women who had at least one urine test that was positive for opioid use of any kind (e.g., including prescribed drugs for medication-assisted treatment, such as buprenorphine, as well as nonprescribed drugs, and illicit drugs, such as heroin) within 30 days prior to participating in the study at Time 1 to the “opioid use” group ($n = 53$). By contrast, we assigned women who produced no opioid-positive urine tests within 30 days prior to participating in the study at Time 1 to the “no opioid use” group ($n = 37$). In addition to urinalysis tests, we also utilized information from medical charts (i.e., physician notes, referral information, prescribed medications) to confirm whether women were initially referred for opioid misuse or medical reasons unrelated to drug use.

Opioid Use Severity During Pregnancy. We created a three-point ordinal variable to assess the severity of participants’ opioid use by evaluating urinalysis tests within 30 days prior to their enrollment in the study, in addition to information from participants’ medical charts (i.e., physician notes, referral information, prescribed medications). This variable provides additional information regarding the nature of women’s opioid use beyond our dichotomous “opioid use” or “no opioid use” variable, ranging from past opioid use but no current use, to current prescribed opioid use only, to illicit drug use including opioid use. Women in the high-risk comparison group were not included. Participants were assigned a score of: a) “1” if all urinalysis samples within the past 30 days were absent of all drugs, but they had previously been prescribed

buprenorphine, methadone, Subutex, or suboxone for medication-assisted treatment at any point during their pregnancy (according to their medical charts) prior to enrollment in the study (*prior opioid use only*), b) “2” if one or more of their urinalysis samples indicated the presence of an opioid that was listed as a prescribed medication in the patient’s medical chart, but no other drugs were present (*current prescribed opioid use*), or c) “3” if one or more of their urinalysis samples indicated the presence of opioids that were not listed as prescribed medications in their medical chart OR if their urinalysis samples indicated the presence of prescribed opioids plus additional non-prescribed medications/substances, such as marijuana, non-prescribed benzodiazepines, or cocaine, according to their medical charts (*current non-prescribed opioid misuse*). We excluded women ($n = 6$) whose urine assays only revealed the presence of illicit drugs other than opioids.

Depression, Anxiety, and Stress. Mothers completed the 21-item short form of the Depression, Anxiety, and Stress Scale (DASS-21; S. H. Lovibond & P. F. Lovibond, 1995). The DASS-21 consists of three subscales – Depression, Anxiety, and Stress – each containing seven items related to the participant’s subjective psychological and somatic experience of depressive symptoms (e.g., “I couldn’t seem to experience any positive feeling at all”), anxious symptoms (e.g., “I was aware of dryness in my mouth,” “I was worried about situations in which I might panic and make a fool of myself”), and stress arousal (“I found it hard to wind down,” “I tended to over-react to situations”). Participants rated each item on a 4-point scale indicating the extent to which they experienced each symptom during the past week, ranging from 0 (“Did not apply to me at all”) to 3 (“Applied to me very much or most of the time”). Three subscale scores for depression, anxiety, and stress are obtained by summing all items for the respective scale, and then multiplying each sum by two in order to match scoring from the long form, the Depression,

Anxiety, and Stress Scale – 42 (DASS-41; P. F. Lovibond & S. H. Lovibond, 1995). Higher scores on each scale indicate greater symptom severity. The present study utilized each of the subscale scores to answer our research questions. The DASS-21 has demonstrated adequate to good internal consistency and convergent validity across clinical (Antony, Bieling, Cox, Enns, & Swinson, 1998; Clara, Cox, & Enns, 2001), nonclinical (Henry & Crawford, 2005), and racially diverse (Norton, 2007) samples. Studies have demonstrated that the three subscales of the DASS-21 are moderately to highly correlated (Antony et al., 1998; P. F. Lovibond & S. H. Lovibond, 1995; Norton, 2007). In the present sample ($N = 90$), Cronbach's alpha for the depression subscale was $\alpha = .93$, for anxiety was $\alpha = .82$, and for stress was $\alpha = .90$. This indicates good internal consistency for each DASS-21 subscale within our overall sample (DeVellis, 2016). Furthermore, all subscales were highly correlated at $p < .001$, consistent with previous studies using the DASS-21. See Table 2.

Neonatal Opioid Withdrawal Syndrome (NOWS). After birth, nurses in the hospital closely monitored infants exposed to opioids in-utero. Infants received Finnegan scores, a scale designed to assess the severity of withdrawal symptoms (Finnegan, Connaughton, Kron, & Emich, 1975), following birth. At the hospital where the study occurred, infants who received two consecutive Finnegan scores of 10 or higher or one Finnegan score of 12 or higher were considered to have NOWS by a medical professional. Subsequently, these infants were admitted to the neonatal intensive care unit (NICU) to treat their withdrawal symptoms (e.g., with morphine or phenobarbital). An obstetrical resident at the hospital utilized this information regarding Finnegan scores and NICU admission to answer a “yes or no” question about whether each infant developed NOWS. Based on this information, we created a dichotomous variable to

assign infants either the “NOWS” group (where infants were assigned a score of “1”) or the “no NOWS” group (where infants were assigned a score of “0”).

Maternal Opioid Detoxification Status at Birth. Uniquely, all patients referred to the high-risk pregnancy clinic for opioid misuse are given three treatment options: 1) to maintain a stable dose of prescription opioid medication to prevent withdrawal symptoms and reduce craving for opioids (referred to as medically-assisted treatment [MAT]; usually consisting of prescribed Subutex or Suboxone); 2) to taper or decrease their dose of prescription opioid medications over time to a very low dose by the time they give birth; or 3) to fully detoxify from all opioids prior to giving birth after tapering their dose of opioid medication over time (which varied based on the patient). We created a categorical variable indicating women’s opioid treatment status at delivery of their infants, called “opioid treatment outcome.” We assigned participants a “1” if they were on prescribed doses of medication-assisted treatment (*MAT group*; $n = 21$), a “2” if they had tapered to a dose below the dose prescribed for medication-assisted treatment (*taper group*; $n = 13$), and a “3” if they had detoxified from opioids completely by the date of delivery (*detoxification group*; $n = 19$). Given that our sample was small and there was an uneven distribution of babies born with NOWS across treatment groups (i.e., the detoxification group had no variability in terms of NOWS and the MAT group had very little variability – See Table 5), we recoded our three-level categorical variable to create a dichotomous variable called “opioid detoxification status” by collapsing the taper and detoxification groups into a single category. This dichotomous variable was used in our main analyses. We combined these two groups because women who detoxified from opioids went through a similar process of tapering before achieving full detoxification. For this dichotomous variable, we assigned participants a “0” if they maintained on MAT throughout pregnancy to the time of birth (*MAT group*, $n = 21$),

and a “1” if they gradually tapered to a lower prescribed dose during their pregnancy or if they had detoxified from opioids by the date of delivery (*tapered/detoxified group*; $n = 32$).

Gestational Age. We recorded the number of weeks women were pregnant before giving birth to their infants. This information allowed us to assess and control for whether infants were born pre-term or full-term. There were no significant differences between groups in terms of gestational age at delivery. See Table 1.

CHAPTER THREE

RESULTS

Preliminary Analyses: Demographic Differences Between Groups

Independent samples *t*-tests and chi-square tests of homogeneity were conducted in order to assess differences between groups among our continuous (i.e., age, gestation, gestational age) and categorical variables (i.e., employment status, whether mother identified with an ethnic minority group, had a partner), respectively. There were significant differences between women who used opioids during pregnancy and women with high-risk pregnancies for reasons unrelated to drug use in terms of age, such that women in the opioid use group were older than women in the no opioid use group, $t(88) = -3.26, p < .01$, and whether they identified with an ethnic minority group, such that women in the no opioid use were more likely to identify with a minority ethnic background than women in the opioid use group, $\chi^2(1) = 7.72, p < .01$. Thus, we controlled for these variables in our analyses using the full sample ($N = 90$). However, there were no group differences in terms of employment status, relationship status (i.e., whether women reported having a partner or not), or gestation (i.e., number of weeks into pregnancy) at the time of enrollment in the study, so we did not control for these variables. On average, participants carried their infants to full term. See Table 1.

We additionally ran preliminary correlations and chi-square analyses to assess relationships among each of the variables in our main analyses. Table 2 details correlations among variables that were examined within the overall sample ($N = 90$). Table 3 lists correlations among variables that were examined within the opioid use group only ($n = 53$). We conducted Pearson's correlations to assess relationships among our continuous variables, point-biserial correlations to assess relationships between continuous and dichotomous variables, and

Spearman's correlations to assess relationships between ordinal and continuous variables. Table 4 reports the linear-by-linear association resulting from a chi-square analysis which assessed the distribution of NOWS in the context of our ordinal opioid use severity variable at Time 1 ($n = 53$). Finally, Table 5 details the distribution of NOWS among each of the three levels of opioid treatment outcome (i.e., MAT, taper, detoxification) at Time 2 ($n = 53$). Given the significant correlation between maternal opioid detoxification status at Time 2 and infants' NOWS outcomes (See Table 3) and given that NOWS is a unique consequence of opioid use during pregnancy, we decided to control for this variable in our analyses when assessing other possible factors contributing to NOWS development.

Hypothesis 1: Differences in Anxiety, Depression, and Stress Between Groups

To test our first hypothesis, that women in the opioid use group would report significantly higher symptoms of depression, anxiety, and stress than women in the no opioid use group, we conducted a one-way multivariate analysis of covariance (MANCOVA). This method allowed us to examine differences between groups in terms of anxious, depressive, and stress symptoms simultaneously, given that these constructs were highly correlated in our sample (See Table 2). We entered our dichotomous group variable (opioid use group or no opioid use group) as the independent variable and depression, anxiety, and stress as dependent variables. We entered maternal age and ethnicity as covariates. Consistent with our hypothesis, there was a significant main effect of group on depression, anxiety, and stress, $F(3, 84) = 3.99, p = .01$, Wilks's Lambda = .88, partial $\eta^2 = .13$. Means and adjusted means indicated that depression, anxiety, and stress tended to be higher in the opioid use group than in the no opioid use group (See Table 6). There was no main effect for maternal age, $F(3, 84) = 2.13, p = .10$, Wilks's

Lambda = .93, partial $\eta^2 = .07$, or ethnicity, $F(3, 84) = .69, p = .56$, Wilks's Lambda = .98, partial $\eta^2 = .02$.

We conducted univariate analyses of covariance (ANCOVAs) post-hoc to determine group differences between depression, anxiety, and stress separately. A Bonferroni adjustment for multiple comparisons was made such that values would be accepted as significant when $p < .017$. Depression [$F(1, 86) = 11.61, p = .001$, partial $\eta^2 = .12$], anxiety [$F(1, 86) = 4.20, p < .05$, partial $\eta^2 = .05$], and stress [$F(1, 86) = 7.85, p < .01$, partial $\eta^2 = .08$] were significantly different between groups, as predicted. We then examined pairwise comparisons to determine differences between adjusted means between groups after accounting for covariates. See Table 7. Stress was significantly greater in the opioid use group than in the no opioid use group, with an adjusted mean difference of 6.35, 95% CI [1.84, 10.85], $p < .01$. Adjusted mean differences for depression (8.07, 95% CI [3.36, 12.79], $p = .001$) and anxiety (4.29, 95% CI [.13, 8.44], $p < .05$) were also significantly greater in the opioid use group than in the no opioid use group.

Hypothesis 2: Depression, Anxiety, and Stress Predicting NOWS

To test our second hypothesis, that higher reported symptoms of maternal depression, anxiety, and stress during pregnancy would predict the presence of NOWS in infants born to mothers in the opioid use group ($n = 53$), we first conducted a binomial logistic regression (See Table 8). In this analysis, we controlled for our dichotomous opioid detoxification status variable (i.e., MAT or taper/detoxification) at Time 2. We began by controlling for this variable instead of the three-level opioid treatment outcome variable (i.e., MAT or taper or detoxification) because the group of women who detoxified from opioids was a constant, meaning there was no variability in NOWS development that could be explained within this group (See Table 5).

Additionally, it is important to note that when we ran this analysis and each of the following regression analyses, we initially controlled for the opioid use severity (Time 1) variable. Despite the nonsignificant relationship between opioid use severity and NOWS as assessed by a chi-square analysis (See Table 4), studies suggest that the severity and timing of opioid use during pregnancy can account for differences in NOWS development (ACOG, 2017, August) and this was the best measure we had in this study to control for the intensity of opioid use at another time point during pregnancy in addition to at the time of birth. However, this variable did not emerge as a significant predictor of NOWS in any of our analyses, and it did not change our results. Thus, the analyses presented below do not include this variable.

The first step of our binary logistic regression, in which opioid detoxification status was entered a covariate, was significant, $\chi^2(1) = 24.26, p < .001$. This first step of the model explained 49% of the variance in whether infants developed NOWS according to Nagelkerke R^2 , with 81% of cases being correctly classified. The second step, in which we entered our independent variables – depression, anxiety, and stress, was also significant, $\chi^2(3) = 12.95, p < .01$. The overall model was significant, $\chi^2(4) = 37.21, p < .001$, and it explained 67% of the variance overall in whether infants were born with NOWS according to Nagelkerke R^2 , with 85% of cases being correctly classified. Opioid detoxification status, stress, and anxiety emerged as significant predictors of NOWS. Specifically, MAT and high maternal anxious symptoms during pregnancy were both significantly associated with an increased likelihood of infants developing NOWS, as expected. Interestingly, high maternal stress symptoms during pregnancy were associated with a decreased likelihood of NOWS, contrary to our hypothesis. Depression was not a significant predictor of NOWS. Collinearity diagnostics did not indicate issues with

multicollinearity, despite high correlations between depression, anxiety, and stress. Tolerance values were acceptable, ranging from .52 to .60.

Next, we conducted another binary logistic regression with maternal prenatal depression, anxiety, and stress predicting whether infants were born with NOWS, this time excluding women who detoxified from opioids completely at Time 2 (See Table 9), given that none of the infants in the detoxification group ($n = 19$) was born with NOWS (See Table 5). In this model, we created a dummy variable where we coded participants on MAT as “1”, and women who tapered as “0.” This dummy variable represented maternal opioid treatment outcome, with women who tapered as the reference group. We entered this variable as a covariate in the first step of the regression, which was significant, $\chi^2(1) = 4.04, p < .05$. This step explained 18% of the variance in whether infants were born with NOWS according to Nagelkerke R^2 , with 79% of cases being correctly classified. The second step of the model, in which we entered depression, anxiety, and stress, was also significant, $\chi^2(3) = 12.30, p < .01$. The overall model was significant, $\chi^2(4) = 16.34, p < .01$, explaining 60% of the variance in whether infants were born with NOWS according to Nagelkerke R^2 , with 94% of cases being correctly classified. Again, MAT was the predictor most highly associated with infants developing NOWS. Maternal stress symptoms also emerged as a significant predictor of NOWS, such that lower stress was associated with a higher likelihood of infants developing NOWS. High maternal anxious symptoms marginally significantly predicted NOWS development. Maternal depressive symptoms, again, did not significantly predict NOWS in infants. Thus, as in our previous analysis, our hypothesis was only partially supported.

Post Hoc Analyses: Depression, Anxiety, and Stress Predicting NOWS within Opioid Detoxification Status Groups

Given that opioid detoxification status emerged as the strongest predictor of NOWS in each of our regression analyses, followed by stress and anxiety, we conducted additional post hoc analyses to further examine the relationships between these predictors and NOWS. First, we attempted to conduct another binary logistic regression with moderation in order to assess for potential moderating effects of opioid treatment on the relationship between prenatal maternal depression, anxiety, stress, and infant NOWS development. In this model, we entered depression, anxiety, stress, and dummy variables representing the three levels of opioid treatment outcome (i.e., MAT, taper, and detoxification) as predictors, along with interaction terms for each of these variable pairs, as predictors of NOWS within our opioid use sample ($n = 53$). However, due to the uneven distribution of NOWS within our sample (See Table 5) and our small sample size, the model was not viable. We also attempted to run this model within MAT and taper groups only ($n = 34$) with dummy variables for MAT and taper entered with depression, anxiety, and stress, as well as interaction terms for each variable pair. Again, we were unable to run this model due to the nature of our data.

Given that there was significantly more variability in whether women in the taper/detoxify group gave birth to infants who developed NOWS (25% of infants born with NOWS), $\chi^2(1) = 21.75, p < .001$, while women on MAT demonstrated very little variability in terms of NOWS (91% of infants born with NOWS), and since we could not successfully conduct moderation analyses, we conducted an additional binary logistic regression (See Table 10) within the group of women who tapered or detoxified completely from opioids by the time of delivery ($n = 32$). We utilized the combined group in this regression, as we did not have enough power

within the taper group alone ($n = 13$) to run this analysis. We entered depression, anxiety, and stress as predictors of NOWS simultaneously within a single step in this model. The overall model was significant, $\chi^2(3) = 10.47, p < .05$, and it explained 41% of the variance in whether infants were born with NOWS according to Nagelkerke R^2 with 78% of cases being correctly classified. Consistent with our initial logistic regression, stress and anxiety once again emerged as significant predictors of NOWS development, such that low maternal stress symptoms and high anxious symptoms contributed to an increased likelihood of infants developing NOWS.

Finally, to determine whether symptoms of stress and anxiety explained some of the variability in whether women on MAT delivered babies with NOWS, we conducted a final binary logistic regression (See Table 11) within the MAT group only ($n = 21$). Again, we entered depression, anxiety, and stress as predictors of NOWS simultaneously within one step. The overall model was nonsignificant, $\chi^2(3) = 4.76, p = .19$, explaining 44% of the variance in whether infants were born with NOWS according to Nagelkerke R^2 with 95% of cases being correctly classified. None of these variables significantly predicted NOWS development within this group. It is important to note that although the variance explained by this model is similar to that of the previous model conducted within the taper/detoxification group, it was not significant. Again, this is likely a result of our unevenly distributed sample in terms of NOWS, as well as our limited sample size of 21 participants in this group.

CHAPTER FOUR

DISCUSSION

Findings of the present study indicate that symptoms of depression, anxiety, and stress were significantly higher among women who misused opioids than among women who had high-risk pregnancies for reasons unrelated to drug use, which supported our first hypothesis. Our second hypothesis was partially supported, as high anxious symptoms and low stress symptoms emerged as significant predictors of NOWS development. Depressive symptoms, however, did not significantly predict NOWS. Interestingly, post hoc analyses revealed that the results of our second hypothesis were only supported within the group of women who tapered to a low dose of opioids throughout their pregnancy. We discuss the implications of these findings below.

Depression, Anxiety, Stress, and Opioid Use

Overall, we found that depression, anxiety, and stress symptoms were higher in women who misused opioids during pregnancy than in women with high-risk pregnancies for reasons unrelated to drug use. These findings are consistent with commentary presented in a publication by the American College of Obstetrics and Gynecology in 2017, as well as various additional studies that have demonstrated that anxious and depressive disorders are highly prevalent among women misusing opioids during pregnancy compared to pregnant women in general. By examining anxious and depressive symptoms along a continuum, however, the present study further demonstrated that women who misuse opioids exhibit greater symptom severity than women with medically high-risk pregnancies for reasons unrelated to drug use, who have also been shown have high prevalence rates of anxious and depressive disorders. Thus, not only are

depression and anxiety more prevalent in pregnant women who misuse opioids, but at a dimensional level, their symptom expression may be more severe than pregnant women who do not misuse opioids.

Furthermore, stress has been an under-studied construct in women who misuse opioids during pregnancy, specifically. Findings of the present study indicate that stress is an important mental health concern for future research to focus on within this population, as the severity of stress symptomatology within pregnant women using opioids was significantly higher than women with medically high-risk pregnancies for other reasons.

These findings are particularly important given the nature of our comparison group. Not only does the literature suggest that women with high-risk pregnancies experience significant depression, anxiety, and stress, but the women in the present study's comparison group were receiving medical care for other serious and potentially life-threatening medical conditions, ranging from multiple gestation to heart or blood diseases (e.g., hypercoagulability). Thus, beyond experiencing higher symptoms of depression, anxiety, and stress than pregnant women in general, the current results provide evidence that pregnant women who misuse opioids are more depressed, anxious, and stressed even than women who are at high risk for experiencing these symptoms due to other dangerous medical conditions.

Higher depression, anxiety, and stress symptoms within pregnant women misusing opioids may be due to the unique stressors that they face as a result of their opioid use. Women are often referred to high-risk obstetrical clinics and opioid clinics to seek treatment for their drug use in order to improve their own health, promote their unborn babies' health, and avoid potential involvement with child protective services, which introduces a variety of stressful challenges. For instance, women may decide to decrease and control their opioid use, or detoxify

from it altogether, which is an inherently stressful experience (Gilfillan, Dannatt, Stein, & Vythilingum, 2018). Furthermore, mothers must regularly visit these specialized obstetrical clinics to receive treatment, which can publicly expose them to stigma surrounding their drug use, resulting in feelings of shame (Corrigan & Nieweglowski, 2018; Howard, 2015). Women may even feel that their healthcare providers negatively judge or label them throughout the treatment process (Howard, 2015). It was only recently that the state of Tennessee eliminated the “fetal-assault” law, which criminalized women for using substances during pregnancy (Hui, Angelotta, & Fisher, 2017), which in itself could cause mothers to feel depressed, anxious, and stressed about what will happen to them and their babies after giving birth. On top of these challenges, each of the women in our sample received Medicaid, indicating that they had low socioeconomic status. Research has suggested that struggling with low socioeconomic status, finances and transportation can themselves manifest as treatment barriers (Goodman, 2015; Metz, Brown, Martins, & Palamar, 2018). Taken together, these unique challenges of opioid misuse during pregnancy may help to explain our findings that pregnant women who misuse opioids report significantly higher symptoms of depression, anxiety, and stress than women with medically high-risk pregnancies.

For women who misuse opioids during pregnancy, higher symptoms of depression, anxiety, and stress may have important implications for parenting and infant outcomes. Women naturally experience a growth of grey matter in the brain during pregnancy, which biologically prepares them to experience reward when caring for their child (Rutherford, Potenza, & Mayes, 2013). For mothers who use substances during pregnancy, however, research suggests that this growth in gray matter is stunted, increasing mothers’ risk for experiencing greater parenting stress (Rutherford et al., 2013). Mothers who use substances during pregnancy may lack

effective skills to attend to their child's needs, increasing risk for emotion regulation difficulties, drug-seeking behaviors, relapse, and engagement in maladaptive parenting strategies such as child abuse or neglect (Nair, Schuler, Black, Kettinger, & Harrington, 2003; Rutherford et al., 2013; Suchman et al., 2017). Experiencing prenatal depression, anxiety, stress, and additional environmental stressors may exacerbate parenting stress and its associated risk factors (Chaplin & Sinha, 2013; Gentile, 2017; Milgrom & McCloud, 1996). For infants, maternal emotion dysregulation, relapse, and maladaptive parenting can lead to increased emotional reactivity (Nolvi et al., 2016), disorganized attachment (Hayes, Goodman, & Carlson, 2013), decreased cognitive function (Barker, Kirkham, Ng, & Jensen, 2013), and increased risk for internalizing problems (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002). Moreover, such difficulties in infants may then contribute to increases in parenting stress, potentially perpetuating this cycle of parenting difficulties, substance use, and adverse developmental outcomes for children. Thus, it is important to consider prenatal maternal depressive, anxious, and stress symptoms as treatment targets within the present population, even if women do not have formal diagnoses of a mood or anxiety disorder.

Depression, Anxiety, Stress, and NOWS

Importantly, results of the present study indicated that anxious and stress symptoms accounted for some of the variance in whether infants developed NOWS, but only when their mothers gradually tapered to lower doses of prescribed opioids throughout pregnancy by the time infants were born, as there was more variability within this group in terms of the development of NOWS. It is important to note, however, that none of the infants whose mothers detoxified from opioids were born with NOWS, so this variability is accounted for by the taper group alone. We

combined these two groups in order to have more power to detect variability within the taper group, given that women who detoxified from opioids went through the tapering process, as well, but there was no variability to be explained within the latter group. Within the group of women who maintained a higher, stable dose of prescription opioids throughout pregnancy (i.e., engaged in MAT), there was little variability which could be explained by factors other than opioid use, as 91% of their infants developed NOWS. Thus, anxious and stress symptoms were significant factors influencing the development of NOWS in women who tapered to lower doses of opioids throughout pregnancy, but not for women on who maintained a stable dose of opioids via MAT throughout pregnancy or for women who completely detoxified from opioids prior to giving birth.

Consistent with our hypothesis, more anxious symptoms were associated with a greater likelihood of infants developing NOWS within the present sample. This study expands upon the research conducted by Faherty, Matone, Passarella, and Lorch (2018) by prospectively demonstrating that prenatal maternal anxious symptoms, as opposed to categorical diagnoses, predict NOWS development in infants. This finding indicates that women need not have a formal diagnosis for their anxiety to predict some of the variance in whether their infants will go on to develop NOWS; rather, self-reported anxious symptoms alone seem to explain some of this variance. Given that this is the first study to demonstrate a link between high prenatal maternal anxious symptoms and NOWS, additional research is needed to replicate this finding.

Results of the present study are important, as they may introduce an important place for intervention for women's mental health care, as well as preventative health care to reduce the likelihood of infants developing NOWS when women are tapering from opioid use during pregnancy. Anxiety has recently been implicated as an important treatment target for individuals

with opioid use disorder, given that there is a reciprocal relationship between anxiety and opioid use (McHugh et al., 2017). As such, individuals may engage in opioid use in order to modulate their anxiety (McHugh et al., 2017; Rigg & Ibañez, 2010). Additionally, it is important to consider that maternal use of benzodiazepines and other anxiolytic medications in addition to opioids during pregnancy have been shown to contribute to the development of NOWS (ACOG, 2017, August). Given the current findings, then, it is possible that anxious symptoms influence the development of NOWS in infants via their mother's increased opioid use during pregnancy to attempt to decrease their own anxiety. Furthermore, anxiety is associated with increased risk for various adverse birth outcomes (e.g., preterm birth, low birth weight), which has been hypothesized to be related to increased hypothalamic pituitary adrenal (HPA) axis activity and hormonal increases, such as cortisol (for reviews, see Alder et al., 2007; Ding et al., 2014). These may be possible mechanisms contributing to increased risk for infant NOWS development for mothers reporting higher anxious symptoms. Additional research is needed to further examine these possible pathways.

Interestingly, stress symptoms were significantly inversely associated with the presence of NOWS, such that higher stress symptoms were associated with a decreased likelihood of infants being born with NOWS. This directly contradicted our hypothesis that high stress would be associated with a greater likelihood of NOWS, given that stress is highly associated with substance use in pregnant women (Chaplin & Sinha, 2013). However, this finding is important to consider, especially given that research has not yet begun to examine this link. It is possible that in the present sample, women who reported more stress were taking lower doses of opioids than women who were reporting less stress and were getting closer to detoxifying from opioids than others who had just begun tapering. This would make sense, given that tapering/detoxifying from

opioids during pregnancy under the supervision of an obstetrician is associated with a decreased likelihood of developing NOWS if they continued to engage in behavioral management after detoxification in order to prevent relapse, but it is an inherently stressful experience (Bell et al., 2016). On the other hand, women who experienced less stress may have been taking higher prescribed doses of opioids or continued to misuse drugs, limiting instances in which they might have experienced stressful withdrawal, but potentially alleviating their emotional and physiological experience of stress. Again, further research is needed to elucidate this relationship.

Finally, depressive symptoms did not significantly predict NOWS, in contrast with our hypothesis. While studies have suggested that maternal mood and depressive disorders during pregnancy are linked to NOWS development or symptoms of opioid withdrawal in infants at birth (Faherty et al., 2018; Hensley et al., 2018), it is possible that self-reported depressive symptoms were not enough to explain any variance in the development in NOWS. Another possible explanation of this finding is that pregnant women within the present opioid using sample who reported high rates of depression may have received effective treatment to achieve symptom reduction by the end of their pregnancy. Nevertheless, while depressive symptoms were high among women in our sample, these symptoms did not appear to be associated with infant outcomes.

For each of the present findings, it is important to consider the small sample size, which may have influenced our findings. Additional research is needed to better understand the mechanisms by which maternal anxiety increases the likelihood of infants developing NOWS and maternal stress decreases the likelihood of NOWS, especially in the context of women who are in the process of tapering to lower doses of opioids during pregnancy. This is important, as

the current findings provide support for symptoms of anxiety and stress as factors that explain some of the variability in NOWS development, in support of the biopsychosocial model (Engel, 1977). Thus, they may be important treatment targets to consider in order to achieve optimal outcomes for both mothers' mental health and infants' health and development when mothers are tapering or detoxifying from opioids.

Strengths and Limitations

The present study demonstrated three specific strengths. First, we recruited a sample of women who misuse opioids in pregnancy that is typically challenging, and we measured constructs that are difficult to assess with complete accuracy (e.g., opioid use severity). Second, we examined depression and anxiety as continuous variables based on self-reported symptoms as opposed to limiting the focus to categorical diagnoses only, demonstrating that differences in depression, anxiety and stress between groups, as well as relationships with NOWS development, can be detected at the symptom level. Examining our constructs in this way not only contributed to greater power to detect differences between groups and effects in predicting NOWS, but administering self-report measures is generally easier in prospective studies than obtaining diagnostic information. Finally, we examined differences in stress between groups, which has been largely overlooked in studies of anxiety and depression in pregnant women misusing opioids and NOWS outcomes for their infants.

There were also several limitations in the present study which fall into two main categories – a) sample size and characteristics, and b) measurement issues. Regarding the small sample size used in this study, the ability to accurately detect effects and to generalize to broader populations of women misusing opioids during pregnancy or who had medically high-risk

pregnancies is limited. We were additionally limited in the analyses we were able to conduct within the present sample. With a larger sample size, we would have been able to conduct more complex analyses that would address the complex inter-relationships among mothers' opioid detoxification status, their symptoms of depression, anxiety, and stress, and infants' NOWS outcomes (e.g., path analyses, moderation analyses). Characteristically, women in this sample were mostly white, and they all received Medicaid, indicating low socioeconomic status. This also decreases the ability of these findings to generalize to broader populations.

In terms of measurement issues, women in the present sample participated during different times in their second and third trimesters of pregnancy, which although there were no significant differences between groups on gestation may have confounded their self-reports of depression, anxiety, and stress, depending on how far along they were in their pregnancies, as some studies suggest that there may be variability in these constructs throughout pregnancy (Buist, Gotman, & Yonkers, 2011). Timing may have also been an issue when considering the way in which women were grouped into the "opioid use" or "no opioid use" groups, which we determined groups based on urinalysis samples within 30 days prior to enrollment in the study. Thus, we may have missed some information about women's opioid use prior to that 30-day time period, and with the short half-life of opioids some opioid use would not have been detected. This could potentially lead to misdiagnosis of opioid use severity (i.e., women may have been classified as more or less severe in terms of their opioid use than we assessed them to be). This study lacked information about women's opioid use and other drug use (e.g., illicit drugs, psychotropic medications) throughout pregnancy, which would be important measures to have in order to more accurately predict how much variability depression, anxiety, and stress accounted for in predicting NOWS. Moreover, measuring NOWS as a "yes" or "no" dichotomous variable

is not ideal. It would have been optimal to measure NOWS severity along a continuum based on information about the infant's length of stay in the neonatal intensive care unit (NICU) after birth and dosage of morphine and/or phenobarbital administered to the infant after birth to treat withdrawal symptoms. Finally, this study did not assess medical risk within the opioid use group, which may have influenced our results in terms of between-group differences in depression, anxiety, and stress when compared to women with medically high-risk pregnancies and no drug use.

Future Research

There are several areas in which research can expand upon the current findings. For example, longitudinal studies could examine changes in depression, anxiety, and stress throughout pregnancy in samples of pregnant women who misuse opioids, rather than measuring these constructs at a single time point. Such studies might examine whether there is a specific time during pregnancy at which high anxiety, depression, and stress symptoms are most likely to contribute to the development of NOWS in infants. Longitudinal research might also examine mother and infant outcomes after birth and throughout development in relation to maternal depression, anxiety, and stress symptoms during pregnancy in women who misused opioids.

Furthermore, future research might examine the biological (e.g., comorbid medical conditions) and additional psychosocial factors (e.g., comorbid mental health concerns, social support, socioeconomic status) that contribute to increased depression, anxiety, and stress during pregnancy in women misusing opioids, in addition to exploring the mechanisms by which such symptoms contribute to NOWS development. For instance, studies might examine whether women's social support plays a role in whether their infants develop NOWS, perhaps via

influencing whether women successfully adhere to treatment for opioid use during pregnancy. Our entire sample consisted of women with low socioeconomic status, so additional studies may assess treatment access for women of different socioeconomic status or living in rural vs. urban areas, examining whether access to psychological treatment for opioid-using women with depression, anxiety, and stress is associated with a decreased risk of developing NOWS.

Finally, the present study additionally yielded results that provide a rationale for future studies to further examine the relationship between anxious and stress symptoms and NOWS development in the context of whether pregnant women choose MAT, or to taper to a lower dose of opioids and/or detoxify from opioids completely. Such studies should investigate factors accounting for greater variability in whether infants ultimately develop NOWS when mothers taper or detoxify from opioids prior to pregnancy compared to when they engage in MAT, including the extent to which opioid dosage and detoxification timing during pregnancy account for NOWS development, as well as how much anxious and stress symptoms account for NOWS development within a larger sample that accounts for the details of mothers' opioid use treatment.

Clinical Implications

Findings of the present study may have important clinical implications. For example, significant findings from our assessment of self-reported anxiety, depression, and stress symptoms within the present sample may aid in informing screening procedures in obstetrical clinics. Such screening methods will likely contribute to more effective treatment strategies by helping to support pregnant women misusing opioids and involve them in necessary integrated care, as the present study demonstrated that prenatal maternal anxious and stress symptoms alone

were predictive of NOWS development – women did not need to have formal diagnoses. The Depression Anxiety Stress Scale – 21 (DASS-21) used in this study is a short, self-report measure that is freely available to use, has been well-established in the literature, and assesses depression, anxiety, and stress symptoms on a dimensional scale with recommended clinical cutoff scores ranging from mild to extremely severe (Lovibond & Lovibond, 1995). There is evidence to suggest that the DASS-21 is an effective screening tool for predicting depressive disorders in samples of individuals struggling with substance abuse (Beaufort, De Weert-Van Oene, Buwalda, de Leeuw, & Goudriaan, 2017). Given this information, the DASS-21 would likely be a suitable screening measure to use in opioid clinics, high-risk pregnancy clinics, and other medical settings serving pregnant women struggling with opioid misuse that may help to quickly and efficiently identify women with comorbid depression, anxiety, and stress symptomatology in need of mental health treatment and connect them with the appropriate resources needed to support mothers, prepare them for parenting, and prevent adverse outcomes for their infants, such as developing NOWS.

This is important, given research suggesting that several treatment barriers exist for women who struggle with opioid use disorders during pregnancy, including transportation issues, financial difficulties, and other psychiatric comorbidities (Goodman, 2015; Metz et al., 2018), as well as the fear of being stigmatized for their drug use (Corrigan & Nieweglowski, 2018; Howard, 2015). Furthermore, if women have access to medical care for their opioid use during pregnancy, it does not necessarily mean that they are also receiving adequate mental health care. Therefore, it is likely that not all pregnant women who seeking medical treatment for their opioid use have had access to the resources that would have been needed in order to inform a diagnosis of an anxious or depressive disorder. Moreover, without effective screening procedures, it is

possible that some women may continue to go undiagnosed and untreated for their comorbid mental health concerns, potentially contributing to adverse infant outcomes and parenting stress.

Conclusion

Women who misuse opioids during pregnancy are at risk for experiencing greater symptoms of depression, anxiety, and stress compared to women who have medically high-risk pregnancies for reasons unrelated to drug use. Furthermore, maternal symptoms of anxiety and stress during pregnancy are linked to NOWS development in infants born to women who gradually taper to lower doses of opioids before giving birth. These findings have important implications at a multidisciplinary level (e.g., relevant for medical professionals, mental health professionals, etc.). Specifically, they may inform effective treatment for women who use opioids during pregnancy, as well as prevention efforts for their infants' health and development. For example, effectively screening for depression, anxiety, and stress in health care settings may help more women gain access to necessary mental health care and resources for parenting preparation, which may aid in their treatment success. Furthermore, addressing factors that contribute to mothers' anxiety and stress while they are tapering from opioids during pregnancy may decrease the likelihood that their infants develop NOWS after birth and increase their chances of experiencing healthy development. Thus, these findings elucidate important opportunities for integrated health care to intervene more effectively with mothers and infants achieve optimal psychological, medical, and developmental outcomes.

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APPENDIX

Table 1. *Demographic and Gestation Differences at Time 1 between Opioid Use and No Opioid Use Groups.*

	Overall Sample (<i>N</i> = 90)	Opioid Use Group (<i>n</i> = 53)	No Opioid Use Group (<i>n</i> = 37)	Opioid Use vs. No Opioid Use Groups
Variable	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>t</i>
Age	26.52 (4.58)	27.77 (4.42)	24.73 (4.26)	-3.26**
Gestation (T1)	28.03 (7.75)	28.11 (7.72)	27.92 (7.91)	-.12
Gestational Age (T2)	37.98 (1.57)	38.15 (1.28)	37.75 (1.88)	-1.18
	%	%	%	χ^2
Identifies as Ethnic Minority	17	8	30	7.72**
Employed	18	15	22	0.64
Has Partner	37	38	35	0.06
Medicaid	100	100	100	0.00

***p* < .01.

Table 2. *Correlations among Variables in Overall Sample at Time 1, N = 90.*

	Group (Opioid Use vs. None)	Maternal Age	Ethnic Minority	Stress Symptoms	Anxious Symptoms	Depressive Symptoms
Group (Opioid Use vs. None)	--					
Maternal Age	.33**	--				
Ethnic Minority	-.29**	-.10	--			
Stress Symptoms	.29**	-.06	-.21	--		
Anxious Symptoms	.21*	-.05	-.12	.78**	--	
Depressive Symptoms	.30**	-.13	-.14	.78**	.71**	--

Note. Pearson's correlations were conducted to assess relationships among continuous variables, and point-biserial correlations were conducted to assess relationships between continuous and dichotomous variables.

* $p < .05$; ** $p < .01$

Table 3. *Correlations among Variables in Opioid Use Sample, n = 53.*

	Opioid Use Severity (T1)	Opioid Detox Status (T2)	Gestational Age (T2)	Infant NOWS Status (T2)	Stress Symptoms (T1)	Anxious Symptoms (T1)	Depressive Symptoms (T1)
Opioid Use Severity (T1)	--						
Opioid Detox Status (T2)	--	--					
Gestational Age (T2)	-.01	.15	--				
Infant NOWS Status (T2)	--	-.64**	-.15	--			
Stress Symptoms (T1)	.23	.03	.01	-.14	--		
Anxious Symptoms (T1)	.29*	.17	-.01	.01	.68**	--	
Depressive Symptoms (T1)	.19	-.05	-.05	.05	.69**	.63**	--

Note. Pearson's correlations were conducted to assess relationships among continuous variables, point-biserial correlations were conducted to assess relationships between continuous and dichotomous variables, and Spearman's correlations were conducted to assess relationships between ordinal and continuous variables.

* $p < .05$; ** $p < .01$

Table 4. *Number of Infants Born with NOWS by Maternal Opioid Use Severity Level at Time 1 (n = 53).*

Infant NOWS Status	Maternal Opioid Use Severity (Time 1)		
	Prior opioid use only (Severity = 1)	Current prescribed opioid use (Severity = 2)	Current non- prescribed opioid use (Severity = 3)
No	3	10	13
Yes	0	11	16

Linear-By-Linear Association: $\chi^2(1) = 1.55, p = .21$

Table 5. *Number of Infants Born with NOWS by Maternal Opioid Treatment Outcome at Time 2 (n = 53).*

Infant NOWS Status	Maternal Opioid Treatment Outcome (Time 2)		
	MAT	Tapered	Detoxified
No	2	5	19
Yes	19	8	0

Pearson's Chi-Square: $\chi^2(2) = 33.45$, $p < .001$

Table 6. Means, Adjusted Means, Standard Deviations, and Standard Errors for Between-Group Differences in Depression, Anxiety, and Stress.

Group	Psychological variable					
	Depression		Anxiety		Stress	
	<i>M (SD)</i>	<i>M_{adj} (SE)</i>	<i>M (SD)</i>	<i>M_{adj} (SE)</i>	<i>M (SD)</i>	<i>M_{adj} (SE)</i>
Opioid Use	14.98 (11.13)	15.59 (1.44)	13.28 (9.18)	13.45 (1.27)	18.83 (9.60)	18.99 (1.38)
No Opioid Use	8.37 (8.92)	7.51 (1.75)	9.41 (8.35)	9.17 (1.55)	12.86 (9.89)	12.64 (1.67)

Note. Adjusted means based on Bonferroni correction.

Table 7. *Pairwise Contrasts for Adjusted Means for Depression, Anxiety, and Stress in Opioid and No Opioid Groups.*

Variable	Difference in adjusted means (95% CI)
	<i>Opioid Use vs. No Opioid Use</i>
Depression	8.07 (3.36, 12.79)*
Anxiety	4.29 (.13, 8.44)*
Stress	6.35 (1.84, 10.85)*

Note. *Significant difference ($p < .0167$) based on Bonferroni correction; 95% confidence interval based on Bonferroni correction

Table 8. *Binary Logistic Regression for Maternal Depression, Anxiety, and Stress Predicting NOWS Outcomes in Opioid Use Group (n = 53).*

	<i>B</i>	SE	Wald	<i>df</i>	<i>p</i>	Odds Ratio	95% CI for Odds Ratio	
							Lower	Upper
Opioid Detoxification*	-6.08	1.85	10.85	1	.001	.002	.00	.09
Stress	-.29	.12	5.87	1	.02	.75	.60	.95
Anxiety	.25	.10	6.34	1	.01	1.28	1.06	1.55
Depression	.04	.06	.49	1	.48	1.04	.93	1.16
Constant	4.28	1.51	8.08	1	.004	72.45	--	--

**Note.* We controlled for the dichotomous opioid detoxification status variable in the present model (MAT vs. Taper/Detoxify).

Table 9. *Binary Logistic Regression for Maternal Depression, Anxiety, and Stress Predicting NOWS Outcomes within Women who Received MAT or Tapered from Opioids During Pregnancy (n = 34).*

	<i>B</i>	SE	Wald	<i>df</i>	<i>p</i>	Odds Ratio	95% CI for Odds Ratio	
							Lower	Upper
Treatment Group (MAT vs. Taper)*	5.00	2.32	4.64	1	.03	148.31	1.568	14023.63
Stress	-.39	.18	4.94	1	.03	.69	.48	.96
Anxiety	.24	.13	3.62	1	.06	1.27	.99	1.63
Depression	.10	.08	1.67	1	.20	1.10	.95	1.28
Constant	.05	.77	.004	1	.95	1.05	--	--

*Note. We controlled for treatment group by creating a dummy variable where Taper served as the reference group.

Table 10. *Binary Logistic Regression for Maternal Depression, Anxiety, and Stress Predicting NOWS Outcomes in Women who Tapered or Detoxified from Opioids During Pregnancy (n = 32).*

	<i>B</i>	SE	Wald	<i>df</i>	<i>p</i>	Odds Ratio	95% CI for Odds Ratio	
							Lower	Upper
Stress	-.44	.20	4.93	1	.03	.64	.43	.95
Anxiety	.37	.16	5.84	1	.02	1.45	1.07	1.97
Depression	.06	.09	.48	1	.49	1.06	.89	1.27
Constant	.10	1.03	.01	1	.92	1.11	--	--

Table 11. *Binary Logistic Regression for Maternal Depression, Anxiety, and Stress Predicting NOWS Outcomes in Women on MAT for Opioid Use During Pregnancy (n = 21).*

	<i>B</i>	SE	Wald	<i>df</i>	<i>p</i>	Odds Ratio	95% CI for Odds Ratio	
							Lower	Upper
Stress	-.25	.17	2.17	1	.14	.78	.56	1.09
Anxiety	.05	.13	.15	1	.70	1.05	.81	1.37
Depression	.07	.09	.63	1	.43	1.07	.90	1.28
Constant	6.45	4.43	2.13	1	.15	634.60	--	--

VITA

Samantha Noose graduated from the University of Nevada, Reno in 2016, where she earned a Bachelor of Arts degree in Psychology with an emphasis in Research Specialization, as well as a minor and certificate in Addiction Treatment Services. Following graduation, Samantha worked as a research assistant the University of Nevada, Reno Counseling Center and a Qualified Mental Health Associate at Quest House, a group home for adolescent boys recovering from substance misuse. Samantha was admitted to the doctoral program in Clinical Psychology at the University of Tennessee in 2017. She anticipates earning her Master of Arts degree from the University of Tennessee in August 2019, and her doctoral degree in 2023.