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CORRELATES OF COCAINE USE IN PREGNANCY

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Regina Marie Melendez

2015

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Background: Cocaine is the third most commonly used illicit substance in pregnancy.

Few studies exist to specifically look for correlates of cocaine use in pregnancy.

Objective: To identify correlates of frequency of cocaine use in pregnancy

Methods: We analyzed retrospective data from 50 postpartum women with a history of cocaine use or dependence who participated in a treatment trial for postpartum cocaine use. Study variables included severity of baseline cocaine use, age of onset of use, comorbid mental illness, poly-substance use, trauma and social support history. Data were analyzed using GLMM Negative Binomial Regression.

Results: The strongest correlate of cocaine use in pregnancy was baseline cocaine use six months prior to pregnancy. Daily or greater cocaine use at baseline was associated with a 2.88 increase in the degree of cocaine use in pregnancy ($SD=0.57, p < 0.0001$) on a scale of 0 to 8 measuring frequency of cocaine use. Weekly or greater cocaine use prior to pregnancy was associated with a 2.58 increase in degree of cocaine use ($SD= 0.57, p < 0.0001$). Positive marijuana use in pregnancy was associated with a 1.24 increase in frequency of cocaine use ($SD=0.24, p < 0.0001$). Older age at onset of cocaine use and higher social support scores were both significant, but weakly associated with increased cocaine use in pregnancy. Comorbid mental illness, alcohol use and trauma history were not statistically significant.

Conclusions: This study identified several correlates of heavier cocaine use in pregnancy, and may help guide clinicians in improving screening and directing resources for education of pregnant, cocaine using women.

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TABLE OF CONTENTS

Abstract	i
Acknowledgements	ii
Introduction	
Substance Use in Pregnancy: Scope of the Problem	1
Effects of Cocaine Use In Pregnancy	4
Risk Factors of Substance Use in Pregnancy	8
Risk Factors of Cocaine Use in Pregnancy	9
Statement of Purpose	13
Specific Aim 1: To identify predictors of frequency of cocaine use in pregnancy	14
Specific Aim 2: To describe patterns of cocaine use in pregnancy	15
Methods	
Participants	15
Procedures	16
Measures	17
Statistical Analyses	20
Statement of Responsibility	20
Results	
Participants	21
TABLE 1. Characteristics for $N= 50$ participants	21
Cocaine Use in Pregnancy	22
Figure 1. Cocaine use Trajectory: Cocaine Use Frequency by Month in Pregnancy	23
Correlates of Cocaine Use in Pregnancy	23
TABLE 2. Correlates of degree of cocaine use in pregnancy by NRB analysis	24
Discussion	25
Limitations	30
Clinical Implications	32
References	32

INTRODUCTION

According to the 2013 National Survey of Drug Use and Health (NSDUH), the use of illicit substances in pregnancy has risen substantially over the last decade.¹ This is a critical concern, as there are more deaths, disabilities and illnesses from substance abuse than from any other preventable health condition in the United States.² Data from the 2002-2003 NSDUH, a nationally representative epidemiological survey, found cocaine to be the third most commonly used illicit substance in pregnancy, following marijuana and prescription drug abuse.³ Below we review the literature on the epidemiology and risk factors associated with substance use during pregnancy, with particular attention to cocaine use and subsequent complications for maternal and neonatal health.

Substance Use in Pregnancy: Scope of the Problem

About one in four pregnant women report substance use in pregnancy, with the prevalence of tobacco and alcohol use highest at about 19% and 10% of pregnant women respectively.³ Pregnant women who smoke cigarettes have increased risk of negative pregnancy outcomes, including ectopic pregnancy, premature rupture of membranes, placental abruption, placenta previa and stillbirth.⁴ Tobacco use also imposes risk to the neonate, including preterm birth, low birth weight or intrauterine growth restriction, birth defects such as cleft lip and sudden infant death syndrome (SIDS).⁴ Similarly, alcohol use in pregnancy is associated with poor birth outcomes. Fetal alcohol syndrome is the leading preventable birth defect, with impairments in physical, mental and behavioral development.⁵ Moreover, fetal alcohol spectrum disorder is associated with preterm birth,

low birth weight and failure to thrive, as well as position brain damage, vision and hearing problems and major organ defects.⁶

About 5.4% of pregnant women used illicit drugs in the prior 30 days according to NSDUH from 2012-2013, almost doubling the estimated 3% in 2002.¹ The rates varied substantially by age, with 14.6% illicit use among women aged 15 to 17, 8.6% among women aged 18 to 25 and 3.2% among women aged 26 to 44.¹ These figures are still considered a low estimate, as perceived negative judgment, as well as legal and social consequences, may lead women to underreport use.⁷

Marijuana, the most commonly used illicit drug among pregnant women, has been associated in some studies with intrauterine growth restriction, developmental deficits in childhood and predisposition for future addiction in adolescence.⁸⁻¹⁰ Non-medical use of prescription drugs has increased by 400% since the late 1990s, with opioid related deaths now surpassing deaths from motor vehicle accidents and suicides in the United States.¹¹ In parallel to this increase, non-medical prescription drugs are now second to marijuana use in prevalence in pregnancy.¹ As a consequence, the number of infants born addicted to drugs who develop neonatal abstinence syndrome (NAS) has increased significantly.¹² These infants have dysfunction in the nervous system, manifesting in tremors, irritability, inability to self-soothe, and seizures.¹³ They also have respiratory problems and gastrointestinal dysfunction, and are more likely to be lower in birth weight.¹⁴

According to the National Epidemiological Survey on Alcohol and Related Conditions

(a nation-wide probability sample survey), the 12-month point prevalence for a cocaine use disorder in the general population is 0.27%.¹⁵ This estimate is about one-half that for any use of cocaine, including crack cocaine, in the past month among individuals age 12 or older.¹⁶ Estimates for any use of cocaine in the prior month have remained stable (between 0.5-0.7% of the population) over the past five years.

The reported prevalence of cocaine use in pregnancy varies immensely depending on method of assessment, gestational period of assessment and population characteristics.¹⁷ In a single hospital study (N=462) based in New Orleans, more than 3% of women had a positive urine test for cocaine metabolites,¹⁸ a rate similar to what was found in Florida among urine samples collected from 715 pregnant women.¹⁹ These rates were higher than a probability sample of pregnant women in California that collected over twenty nine thousand urine samples from women and found a rate of 1.1% for positive cocaine tests.²⁰ A study by Savitz et al 2002, estimated the prevalence based on self-report and urine test to be from 2-6%, and hair assays to be around 15% in a prenatal care center in North Carolina. This rate is similar to patients identified by cocaine-positive urine screening in the early 1990s in Boston City Hospital (17%)⁶ and Pinellas County, Florida public health clinics (15%),^{19,21} yet much higher than 0.3%-1% (up to 49,000) estimates based on 2013 NSDUH self-reported data.¹⁶

Given the multiple social and environmental determinants of drug use, variability of the prevalence over time and location is expected. Overall, most reported estimates are reasonably close to national survey estimates of 0.3% to 1% for cocaine use in

pregnancy, though some outliers report much higher use. Cocaine use in pregnancy can thus affect close to 200,000 women every year, and subsequently has an impact on maternal, neonatal and developmental outcomes as well as societal and economic consequences.

Effects of Cocaine Use In Pregnancy

In the 1980s and early 1990s, there was much attention and concern given to cocaine use in pregnancy. With the emergence of crack, a smoke-able, less expensive form of cocaine, there was a change in the demographic of individuals who use cocaine from middle-and upper class young urban professionals to men and women of lower socioeconomic status.²² Crack use by pregnant women led to what was known as an epidemic of “crack babies.” This resulted quickly in public outcry and the initiation of several studies to understand the effects of cocaine in pregnancy. These early studies had findings that more recent studies have found to be exaggerated.²³⁻²⁶ Nonetheless, more controlled, longer-term studies published later have shown that effects of cocaine-exposure are variable, and may be due to a combination of biological effects of cocaine use as well as genetic and environmental factors associated with cocaine use.

Cocaine produces prolonged adrenergic stimulation by blocking the presynaptic uptake of norepinephrine, serotonin and dopamine.^{27,28} While dopamine’s prolonged activity in the limbic system and cortex lead to cocaine’s euphoric effects, the prolonged catecholamine activity results in cardiovascular complications, such as hypertension, tachycardia, and arrhythmias. Myocardial ischemia and infarction can occur as a result of thrombosis or

vasospasm. In pregnancy, there is increased sensitivity to the cardiovascular effects of cocaine²⁹, and maternal complications can include premature labor, placental abruption, uterine rupture, and death.³⁰⁻³² A retrospective case-control study of 200 cocaine-exposed maternal-neonatal pairs from 1991 to 2000 found that cocaine use was correlated with premature rupture of membranes (23% vs 0% p=0.000), preterm delivery (40% vs 6%, p=0.000) fetal demise (5% vs 0% p=0.004), preterm delivery, lower birth weights (2660 vs 3305g p=0.000), more respiratory distress (14% vs 4%, p=0.001), and longer hospital stays (10 vs 3 days, p=0.000).³³ There may also be a dose-dependent effect, such that more cocaine exposure leads to more severe outcomes in head circumference, infant tone and behavior.^{34,35} Literature reviews similarly find that numerous studies report significant increases in these obstetric and neonatal complications in women who use cocaine^{36,37} although the earlier studies showed more robust associations and may not have accounted for the effects of poly-substance use and other confounding factors.²⁶ Indeed, it is difficult to isolate the effect of cocaine use, given cocaine using women also have obstetric risk from correlates of use including inadequate nutrition, higher incidence of sexually transmitted infections and physical abuse.³⁸ However, data from two comprehensive, multicenter prospective investigations comparing women who used multiple substances in pregnancy found that cocaine use was a predominant risk factor for preterm birth, when systematically controlling for other substances and predictors of preterm birth.³⁹

The largest study to evaluate the impact of substance use, in particular cocaine use, in pregnancy- the Maternal Lifestyle Study (MLS), began in the 1990s and is still ongoing

at four research sites (University of Miami, University of Tennessee at Memphis, Wayne State University, and Brown University). In one article published from this study, 717 cocaine-exposed infants were compared with 7448 non-cocaine exposed infants.⁴⁰ Infants that were cocaine exposed on average were 1 week younger in gestational age, 322 g less in weight, 1.7 cm shorter and were 1.0cm smaller in head circumference than the non-cocaine-exposed group. The cocaine-exposed infants also had more central nervous system symptoms (adjusted OR 1.7; 99% CI 1.2-2.2) and infections (OR 3.1; 99% CI 1.8-5.4). Bada et al. went on to report in another study using MLS data that central nervous system signs were highest in infants exposed to both opiates and cocaine.⁴¹

Beyond the risk to infant health from prenatal exposure to drugs, there are increased health risks if mothers continue to use illicit substances postpartum. Children can be exposed to cocaine passively via inhalation. Data from children less than 1 year old found that both upper and respiratory tract infections occur more commonly in children who have positive urine tests for cocaine and its metabolites.⁴² Infants and young children with cocaine positive urine tests are also more likely to be seen in the emergency room and general pediatrician visits than children who do not have positive urine tests for cocaine, controlling for socio-demographic factors.⁴²

The effects of cocaine on parenting, and early childhood through adolescent development have been studied as well. Maternal cocaine use is associated with higher psychological distress in mothers⁴³ and higher rates of abuse and neglect.^{44,45} Cocaine using postpartum mothers are more likely to suffer from depression, stress, paranoia, psychotic symptoms

and anxiety.⁴³ Richardson et al 2008 performed a longitudinal, prospective study of 295 mothers and infants, and found that women who used cocaine in pregnancy rated their infants as more fussy or difficult and inadaptable than women who did not use.⁴⁶ When cocaine-using mothers are evaluated during infant feeding, they are found to be less flexible and have more conflict than mothers who are drug free.⁴⁷⁻⁴⁹ A 2012 review by Nephew et al concluded that cocaine use can drastically affect maternal behavior, thus leading to child neglect and disruption of mother-child bond and subsequent detrimental effects on health and development of offspring.⁵⁰ Observational studies of children and mothers who use cocaine show that mothers with cocaine use have difficulty developing maternal behaviors, such as recognizing infant cues and engaging with their child.^{49,51,52}

The effects of cocaine use during pregnancy on child development are often complicated by other exposures that occur during pregnancy. Nonetheless, Richardson et al found that cocaine use in the second trimester was associated with significantly lower motor development compared to no exposure or exposure during other trimesters, hypothesizing that cocaine exposure affects development through changes in neurotransmitter systems.⁴⁶ Other studies in the past decade have found cocaine exposure to effect early language development^{53,54} as well as have small, but significant effects on adolescent development.⁵⁵ The MLS study mentioned above also followed 1056 children longitudinally to study development, and found that after controlling for confounders (including other drug use) that internalizing, externalizing and total behavior problem scores were higher for high prenatal cocaine exposure than for some or no use, and these results persisted to age seven.⁵⁶

The societal and economic impact of cocaine use is significant. The cost of crime, health related problems and reduced work productivity attributed to cocaine use are nearly \$300 billion US dollars annually.²³ Maternal cocaine use often results in the removal of the infant from custody within the first 18 months of life,⁵⁷ and is the leading cause of infant placement by state welfare agencies.⁵⁸ Minnes et al found that heavier cocaine use, lack of prenatal care, and more severe psychological symptoms all increase the likelihood of loss of custody of the newborn.⁵⁹

Risk Factors of Substance Use in Pregnancy

Numerous studies have explored risk factors for alcohol, tobacco and illicit substance use in pregnancy. Tobacco use in pregnancy is associated with less education, lower socioeconomic status, late or no prenatal care, public or no health insurance, being unmarried, lack of social support, legal problems, mental illness, early age of onset of tobacco use, and having partners who smoke.^{8,60-64} Alcohol use in pregnancy is linked with having partners who have a history of substance use, unwanted pregnancy, previous participation in alcohol or drug treatment programs, as well as late or no prenatal care.⁶⁵ Additionally, women who ascribe greater social importance of alcohol in their lives are more likely to use alcohol in pregnancy.⁶⁶ In contrast to the characteristics of women who use tobacco in pregnancy, those using alcohol have been shown to have higher income, more education and be older in some studies, but concurrent alcohol and tobacco use in pregnancy tends to follow tobacco use in that women are more likely to have less education, low levels of social support and poor mental health.⁶⁷ Illicit substance use in pregnancy is associated with having comorbid mental illness,⁶⁸⁻⁷¹ being unmarried or

unemployed,^{3,72} and identifying as non-Hispanic, White.^{3,65} Illicit substance users in pregnancy are also more likely to use tobacco or other substances during pregnancy.^{69,73,74} Trauma and history of abuse have additionally been linked to illicit drug use in pregnant women.^{75,76}

Risk Factors of Cocaine Use in Pregnancy

Despite what is known of the health, social, and economic consequences of cocaine use in pregnancy, few studies have looked specifically at predictors of cocaine use in pregnancy.

A Toronto, Canada based case-control study of over 1600 women from 1985 to 1990 found that women who had been exposed to cocaine during pregnancy were younger, more likely to be single (60% single women using cocaine vs 38% and 14% in two control groups, $p<0.001$) and have a higher incidence of elective abortion. A high percentage of women who use cocaine endorsed cannabinoid use (46%) and alcohol and cigarette consumption was also higher in the cocaine group. Additionally, both women who use cocaine and the male partners of these cocaine-using women had a significantly lower socioeconomic status ($p<0.001$) than control women or their partners.

Bendersky et al found similar results regarding poly-substance use and environmental risk factors for cocaine use in pregnancy.⁷⁰ Their study of cocaine positive pregnant women in two inner cities (Trenton, NJ and Philadelphia, PA) found that cocaine-positive women were more likely to smoke cigarettes, have less stable living situations, live in

environments where substance use was high, have less social support, rely on public assistance and report family history of alcoholism or drug abuse. In contrast to the results from the Toronto study, Bendersky et al found that individuals who use cocaine tended to be older in age.⁷⁰ Older age as a predictor of cocaine use was also found in later studies, such as Shieh et al. They conducted a cross-sectional study comparing pregnant cocaine/heroin using women with marijuana using women at a prenatal clinic in northeast, United States and found that pregnant heroin or cocaine using women tend to be older (about 6 years older), have experienced more pregnancies, have more severe drug use scores, and have initiated care later than marijuana users.⁷⁷

Kissin et al expanded on these environmental risk factors, especially the nature of social support.⁷⁸ They conducted a descriptive study of characteristics of 240 pregnant opioid and/or cocaine dependent women in Baltimore, MD 1994 and 1995, admitted to treatment. They found that women initiated use ranging from 12 to 38 years old, and over half of women reported drug use was initiated by a friend (53%) followed by a family member (27%) and/or sexual partner (24%). With regards to social support, almost half of women reported having no close friends and 28% reported spending the majority of their free time alone. Cocaine and/or opioid using women who ended up losing custody of their children were more likely to be homeless, have less education, more medical and employment problems, more previous drug treatment episodes and more recent cocaine use.⁷⁸

Beyond the environmental and demographic risk factors associated with cocaine use in pregnancy, few studies have reported on health and psychological risk factors. Strickland et al 1993 reported on a small study of 21 postpartum urban African-American women, 10 of whom had infants who tested positive for cocaine at parturition. Through clinical interviews, they found that a cocaine positive mothers scored significantly higher on depression ($F=4.44, p<0.05$) and sociopathy ($F=13.48, p,0.002$) than cocaine-negative mothers.⁷⁹ A study of 143 postpartum women in a Midwest hospital found that poor, primarily African American urban women who used cocaine in pregnancy were more likely to report increased psychological distress than non-cocaine using women of similar racial and socioeconomic status.⁴³

One case-control study of over 200 pregnant women in Detroit, MI recruited from 1993-1994 similarly found that cocaine using pregnant women had higher depression scores (OR: 1.09, $p<0.05$).⁸⁰ In addition to depression, they found other significant predictors in their regression model, which are in agreement with those of Bendersky et al 1996 and Kissin et al 2006. Cocaine using women who used drugs in pregnancy were more likely to have been introduced to substance use by a male partner (OR: 5.37, $p<0.05$), have a family history of drug or alcohol problems (OR: 3.16, $p<0.05$), endorse less social support (OR: 2.16, $p<0.05$), have less-stable living situations (OR: 1.25, $p<0.05$), and have current partners who were substance users (OR: 1.43, $p<0.05$), compared to women who did not use cocaine in pregnancy.⁸⁰ In addition, they found that poly-substance use was common to all illicit drug users, but in particular those using cocaine. In fact, heavy

cigarette use (at least half-pack per day use) was the single strongest predictor of cocaine and other substance use in pregnancy (OR: 10.8, $p < 0.05$).⁸⁰

As the aforementioned studies all utilized self-report as their primary screening tool, a case-control study published by Savitz and colleagues in 2002 utilized urine assays, postpartum hair assays and self-report to identify cocaine-using women and indicators of cocaine exposure in pregnancy. Through these additional screening methods, they were able to build a large study of over 2600 women in prenatal care in North Carolina, and found strong demographic predictors of exposure. They found a markedly higher prevalence of cocaine use among younger, black, less educated, poorer women. Race, education and income were associated with adjusted risk ratios for cocaine exposure as high as 3 to 6, such that black women with low education and socioeconomic status had a prevalence of 52% exposure using hair assays.

Mitsuhiro and colleagues in São Paulo, Brazil, similarly utilized hair analysis to identify cocaine and marijuana using women in a population of 1000 teenagers in the third trimester of pregnancy. They found that those testing positive for cocaine were mostly from low-income, inner city areas, unmarried, and unemployed and less educated.⁸¹

In summary, few studies have specifically looked at determinants of cocaine use in pregnancy, but those studies from the 1990s to 2010s that have reported on various demographic, social and psychological risk factors have been surprisingly consistent, despite differences in time, location and population. Most agree that family history of

substance abuse, less stable environments, drug use by partners and family, less social support, poly-substance use and depression are associated with positive cocaine use in pregnancy. Identifying these factors is important, as surveillance of illicit drug use is difficult.⁸² Urine toxicology screening is expensive, only sensitive to specific time frames, and tends to be racially motivated.⁸³ Use of hair for assessment is limited by differences in hair texture and color affecting results.⁸² Self-report surveys remain the most prevalent choice for surveillance of drug use,^{2,82} thus targeting screening and improving screening using known risk factors may aid in identifying women who are likely to underreport use.⁸⁴ Though identification of women and improved interventions, we can begin to reduce cocaine related complications of pregnancy for mothers, children and society.

STATEMENT OF PURPOSE

Despite what is known about the potentially harmful effects of drugs during pregnancy, the prevalence of substance use in pregnancy, including alcohol and tobacco, is still greater than 25%.³ The use of illicit substances in pregnancy, in particular, has risen over the last decade, reaching upwards of 5.4% as of 2013.¹ This figure is still considered a low estimate, given that maternal drug use is frequently underreported.⁷

Understanding factors that differentiate women who achieve abstinence from those who continue to use drugs in pregnancy is of great importance to improving screening and targeting interventions to ultimately impact maternal and fetal health outcomes. Multiple studies have described correlates of smoking^{61-64,85}, alcohol^{65-67,86} and general illicit or

poly-substance abuse in pregnancy.^{72,73,78,87,88} Few studies exist to specifically look for predictors of cocaine use in pregnancy.^{22,38,80} Cocaine use in pregnancy, though less prevalent than smoking or alcohol use¹, is associated with poor birth outcomes, including preterm birth, intrauterine growth restriction and low birth weight as well as increased complications during pregnancy, such as placental abruption, and maternal migraines and seizures.⁷ To our knowledge, no studies yet exist to identify factors that may predict level or severity of cocaine use in pregnancy. This information could further guide health providers in focusing limited resources and screening toward those women who are at risk for more severe cocaine use in pregnancy, thereby reaching those at greatest likelihood for detrimental health outcomes. This study will seek to identify factors that predict frequency of cocaine use in pregnancy and discuss implications for health communication and screening.

Specific Aim 1: To identify predictors of frequency of cocaine use in pregnancy

Hypothesis #1: Several factors will be associated with heavier cocaine use in pregnancy

- (1) Severity of cocaine use at baseline (prior to pregnancy) will significantly impact cocaine use in pregnancy, with mild cocaine use at baseline predicting greater abstinence from cocaine use in pregnancy and more moderate to severe use at baseline predicting heavier cocaine use in pregnancy.
- (2) Age at first onset of cocaine use will significantly impact cocaine use in pregnancy, with earlier age of onset predicting heavier cocaine use in pregnancy.

- (3) The presence of a comorbid mental illness, such as major depressive disorder, dysthymia, mania, hypomania, generalized anxiety disorder, or PTSD will predict heavier cocaine use in pregnancy.
- (4) Concurrent use of alcohol, marijuana or other drugs during pregnancy will predict heavier cocaine use in pregnancy.
- (5) Trauma will be predictive of cocaine use in pregnancy, with a history of greater traumatic life events predicting heavier cocaine use in pregnancy.
- (6) Lack of social support from spouses, parents, siblings, relatives, friends and social structures will predict heavier cocaine use in pregnancy.

Specific Aim 2: To describe patterns of cocaine use in pregnancy

Hypothesis #2: Cocaine use will decrease from the first to third trimesters of pregnancy, with the majority of women achieving abstinence by the 9th month of pregnancy.

METHODS

Participants

Participants included 50 postpartum women with a history of cocaine abuse or dependence who were enrolled in a randomized control trial to determine the efficacy of progesterone in decreasing postpartum cocaine use. Participants were recruited from obstetric practices and substance abuse treatment centers in the greater New Haven, Connecticut area as well as by referral from Yale New Haven Hospital, St. Raphael's Hospital of New Haven, and other study participants. Women were eligible if they were

aged 18 and older, spoke English, were less than 3 weeks postpartum at time of intake, and met DSM IV criteria for abuse or dependence of cocaine in the six-months prior to conception or during pregnancy. Women who abused other illicit substances or alcohol were eligible as long as cocaine was their primary drug of abuse. If women were also opiate dependent, they must have been undergoing treatment with methadone or buprenorphine. Because women were enrolled in a trial in which they would be receiving progesterone or placebo, women were excluded if they had a history of a major medical illness that would be a contraindication to treatment with progesterone, such as clinically significant liver disease suspected or known malignancy, thrombophlebitis, or history of clot or embolus. Data collection began in 2010 and concluded in 2013. Approval for the trial was obtained from the Human Investigation Committee at Yale University School of Medicine and from affiliated hospitals, and all participants provided verbal and written consent.

Procedures

Women in this study participated in a randomized control trial examining the use of progesterone to reduce postpartum cocaine use. For treatment and procedure details, see Yonkers, et. al 2014.⁸⁹ All participants completed a computerized intake assessment, in which they retrospectively reported cocaine and other drug use during pregnancy, and answered questions on psychiatric and social history. In addition to the computer assessment, participants met with a researcher who performed the MINI international diagnostic interview⁹⁰. The responses from this initial intake visit, which occurred on average within the first week postpartum, were used in this study to analyze correlates of cocaine use in pregnancy.

Measures

Dependent Variable

The aim of this study was to identify correlates of cocaine use in pregnancy. To elicit cocaine use during pregnancy, participants were asked to retrospectively, self-report on cocaine use and frequency during each month of pregnancy. For example, participants were asked, “Did you use cocaine in the first month of pregnancy?” If participants responded yes, they were asked, “During the first month of pregnancy, how often did you use?” Responses were obtained on the following scale: 0=No Use, 1=less than once a month, 2=about once a month, 3=2-3 times a month, 4=1-3 times a week, 5=4-6 times a week, 6=once daily, 7=twice daily, 8=three or more times daily. The dependent variable was operationalized as the reported frequency of cocaine use for each month of pregnancy.

Independent Variables

The independent variables of interest included: severity of cocaine use at baseline, age at first onset of cocaine use, comorbid mental illness, poly-substance use, lifetime trauma history, and social support.

(1) Severity of cocaine use at baseline was determined by the amount of cocaine use in the 6 months prior to pregnancy. Women were asked, “How often did you use cocaine or crack, on average, during the six months before you became pregnant?” Use amounts were recorded on a scale of frequency of use, with 0= less than once a month, 1=about once a month, 2=2-3 times a month, 3=1-2 times a week, 4=4-6 times a week, 5=once daily, 6=twice daily and 7=three or more times daily. Results were then grouped into

three categories. “Mild use” was operationalized as cocaine use less than once per week (0-2 on the scale), “moderate use” as cocaine use less than daily (3-4 on the scale), and “Severe use” as cocaine use daily or more (5-7 on the scale).

(2) Age at first onset of cocaine use was determined by asking women “How old were you when you first used cocaine or crack?” The number in years from 1-50 was recorded.

(3) Comorbid mental illness was defined as meeting MINI international diagnostic interview criteria for major depressive disorder, dysthymia, mania, hypomania, generalized anxiety disorder, or PTSD.⁹⁰

(4) Poly-substance use was defined as positive report of alcohol, marijuana or other drug use during pregnancy. Women were asked, “During the first month of this pregnancy, did you have a drink of wine, beer or liquor? We understand-you might not have even known that you were pregnant yet. Please answer as accurately as possible.”

(5) Lifetime trauma history was determined by self-report of number of traumatic life events, including sexual, physical and emotional trauma. Women were asked 13 questions relating to traumatic experiences, such as “Have you ever experienced rape, that is, someone had sexual intercourse with you when you did not want to by threatening you or using some degree of force? Have you ever been sexually molested, that is, someone touched you in a way that made you feel uncomfortable? Have you ever experienced serious physical attack or assault? Have you ever been threatened with a

weapon, held captive, or kidnapped?” A final “trauma score” was coded as the total number of positive responses to this series of 13 questions.

(6) Social support was determined using questions from a modification of the Kendler Social Support Inventory, which has been shown to significantly predict depression in pregnant women ⁹¹. 24 items assessed personal relationships with spouse, mother, father, siblings, other relatives and friends. For each relationship domain, participants were asked about frequency of contact and emotional quality of interactions. For example, participants were asked, “How frequently do you and your mother see each other, talk/text on the phone, or communicate by letter or computer (email or social network)?” and responses ranged from 0-5 for frequency of support. Emotional quality of support questions included, “How much does she listen to you if you need to talk about your worries or problems?” “How much does she understand the way you feel and think about things?” and “How much does she go out of her way to help you if you really need it?” Responses ranged from 1-5 for emotional support questions. Finally, 3 items assessed frequency of contact with church groups, clubs/organizations and confidants. A total “social support score” was coded as the composite score of the 27 items in the assessment.

Confounding Variables

Variables that were considered possible confounders, and, therefore, held constant throughout the analysis included age of participant, race of participant, marital status of

participant, employment status of participant and the involvement of the Department of Children and Families within the home.

Statistical Analyses

All statistical analyses were conducted in SAS version 9.3. Multiple models were tried to determine the model that would best fit the varied response types within this complex assessment. Ultimately, the GLMM Negative Binomial Regression model was selected, as it best accounted for correlation within subjects and the high zero-inflated distribution of response variables and is most appropriate for retrospective data. Analyses were conducted using backward selection methods. First, independent variables of interest were tested individually for their potential to be included in the model. Variables that did not significantly affect the frequency of cocaine use in pregnancy or were not clinically relevant were excluded, and a multivariate model was fit with the remaining variables. Different variance-covariance matrix and link function were compared before the model was finalized.

Statement of Responsibility

This researcher, Regina Melendez, was responsible for performing participant recruitment and screening as well as conducting weekly assessments, including intake, treatment and follow-up assessments, with participants from June-August 2012, along with Cristine Hine, LCSW. This researcher operationalized the variables of interest for the study. Xiaoxuan Cai, research assistant at Yale School of Public Health, performed the statistical analysis. Regina Melendez, Xiaoxuan Cai, Kimberly Yonkers, MD and Brian Merry, MPH interpreted the results.

RESULTS

Participants

Table 1 presents an overview of the social, demographic and health characteristics of the 50 participants. Overall, participants were approximately 31 years of age at intake

TABLE 1. Characteristics for $N= 50$ participants

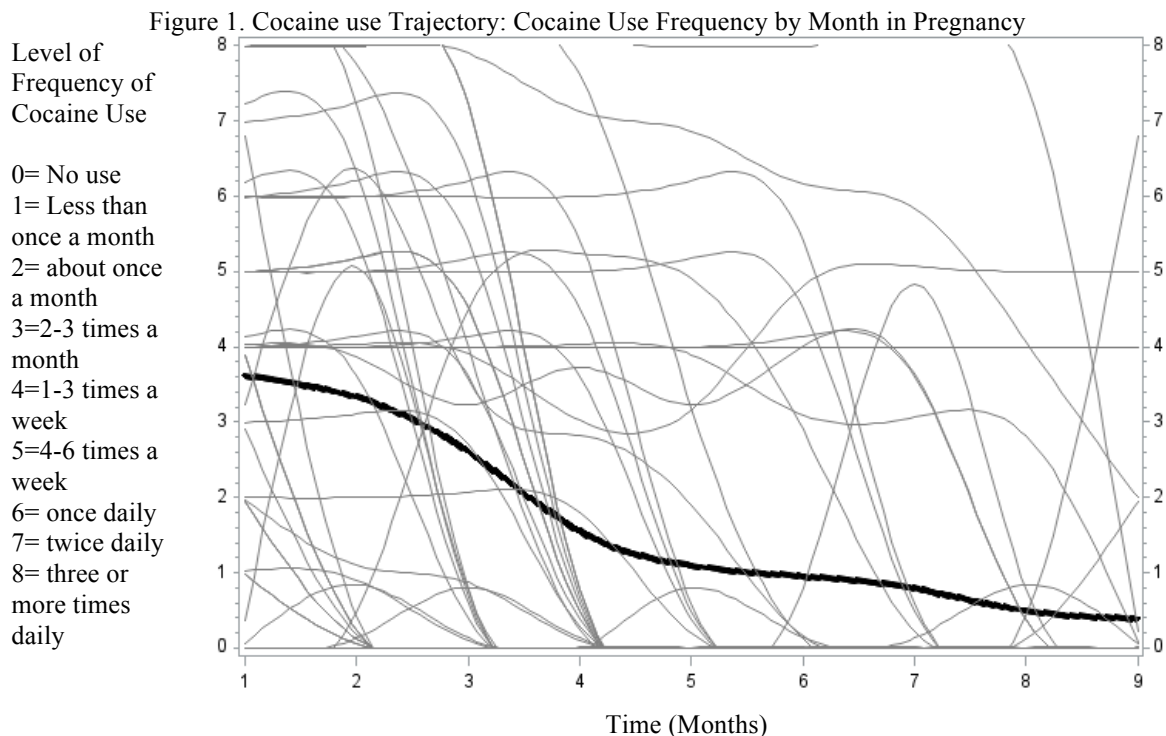
Characteristic	Mean (SD)
Age at Intake	31.5 (5.5)
Education (in years)	12.4 (2.2)
Age at onset of cocaine use	19.9 (5.3)
Social support score	58.9 (23.6)
Trauma score	4.1 (2.4)
	<i>N (%)</i>
Race; Ethnicity	
White; Non-Hispanic	28 (56%)
Black; Non-Hispanic	14 (28%)
White; Hispanic	3 (6%)
Black; Hispanic	4 (8%)
Marital Status	
Married	2 (4%)
Separated/ divorced	8 (16%)
Dating, living together	9 (18%)
Dating, not living together	7 (14%)
Single	24 (48%)
Comorbid Mental Illness	
Major Depressive Disorder	13 (26%)
Anxiety	14 (28%)
PTSD	13 (36%)
Mania or Hypomania	12 (24%)
Dysthymia	24 (48%)
Severity of cocaine use at baseline	
Mild use (< 1/week)	11 (22%)
Moderate use (>1/week, <1/day)	17 (34%)
Severe use (>1/day)	22 (44%)
Poly-substance use during pregnancy	
Alcohol	28 (56%)
Marijuana	21 (42%)
Other drugs	14 (28%)
DCF involvement in household*	20 (40%)
Employed within the last 6 months	10 (21%)

*DCF = Department of Children and Families

($M=31.5$, $SD=5.5$) and had an average of high school level education ($M=12.4$ years, $SD=2.2$). About half of participants identified as Caucasian (56%), with the remaining identifying as Black, non-Hispanic (14%) and Hispanic (14%). More than half of women reported using alcohol or illicit substances during pregnancy, with 56% percent reporting alcohol use, 42% marijuana use, 28% other drug use. The mean age of onset of cocaine use was about 20 years old ($M=19.9$, $SD=5.3$). The mean social support score was 58.9 ($SD=23.6$) with responses ranging from 11 to 119. The mean trauma score was 4.1 ($SD=2.4$) with a responses ranging from 0 to 9.

Cocaine Use in Pregnancy

Figure 1 depicts the cocaine use trajectory of participants from the first to ninth month of pregnancy. Cocaine use overall trended downward as pregnancies progressed. Indeed, negative binomial regression analysis of time in months yielded a coefficient of -0.27 ($SD=0.03$, $p<0.0001$). In other words, every month increase in time was associated with a 0.27 decrease in level of cocaine. Level of frequency/degree of cocaine use was coded on nine different levels, the lowest representing no use and the highest representing three or more times daily usage. By the ninth month of pregnancy 40 women (80% of participants) had achieved abstinence as defined by no cocaine use in the past month. Beyond demonstrating the overall downward trajectory of cocaine use in pregnancy, Figure 1 shows that multiple participants who reported abstinence at earlier months in pregnancy relapsed in later months. Therefore, while overall use decreased, fluctuations month to month were common for multiple participants.



Correlates of Cocaine Use in Pregnancy

Table 2 presents the results of the negative binomial regression analysis examining the relationship between independent parameters and cocaine use in pregnancy. The strongest correlate of cocaine use in pregnancy was baseline cocaine use six months prior to pregnancy. Severe baseline cocaine (daily or greater cocaine use) compared to mild or less than weekly baseline cocaine use was associated with a 2.88 increase in the degree of cocaine use in pregnancy ($SD=0.57, p < 0.0001$). Similarly, moderate baseline cocaine use (weekly or greater cocaine use prior to pregnancy) was associated with a 2.58 increase in degree of cocaine use ($SD= 0.57, p < 0.0001$). Marijuana use was the third strongest correlate of degree of cocaine use in pregnancy, with positive marijuana use in

pregnancy being associated with a 1.24 increase in frequency of cocaine use compared to women who did not use marijuana (SD=0.24, $p<0.0001$).

Age at onset of cocaine use and social support were both statistically significant, but more weakly associated with higher degrees of cocaine use in pregnancy. For each year increase in age of cocaine use onset, there was a 0.13 increase in cocaine use in pregnancy (SD=0.04, $p=0.0017$). Therefore, older ages of onset of cocaine were associated with mildly higher degrees of cocaine usage. For each point increase in social support score, there was a 0.016 increase in cocaine use frequency (SD=0.008, $p=0.0413$). Therefore, for higher reported social support levels, there was a mildly higher degree of cocaine usage. Comorbid mental illness, alcohol or other drug use during pregnancy and lifetime trauma score were not statistically significant and were excluded from the model.

TABLE 2. Correlates of degree of cocaine use in pregnancy by NRB analysis

Parameter	Coeff.	Standard Error	<i>p</i> Value	95% CI
Time	-0.265	0.032	<0.0001	-0.331 - -0.200
Moderate Baseline Cocaine Use	2.583	0.567	<0.0001	1.443-3.723
Severe Baseline Cocaine Use	2.880	0.563	<0.0001	1.749-4.012
Age at Onset of Cocaine Use	0.128	0.039	0.0017	0.051-0.206
Marijuana Use in Pregnancy	1.235	0.237	<0.0001	0.759-1.711
Social Support Score	0.016	0.008	0.0413	0.001-0.032

NRB= negative binomial regression, Coeff. = Negative binomial coefficient

DISCUSSION

According to the *National Survey on Drug Use and Health (NSDUH)*, about 11% of women between the ages of 15 and 44 are currently using illicit drugs, including cocaine.¹ Many of these individuals include women who are considering becoming pregnant, are pregnant or may already be parenting children. Indeed, according to some reports, 5% of pregnant women admit to illicit substance use to care-providers, and this is likely an underestimate of substance use in pregnancy.³ Given what is known about the harmful effects of illicit drugs on the health outcomes of both the mother and newborn, this trend is very concerning. Cocaine use in pregnancy is particularly deleterious, as it holds known risk for significant obstetric complications and increased neonatal morbidity³³ and has been associated with child abuse and neglect⁴⁴, separation of the child from the parent's home^{59,92,93} and delays in development from infancy through adolescence.^{46,53-55,94}

Previous work has shown that women with a history of cocaine abuse or dependence can drastically decrease their use during pregnancy. In one study of cocaine use in pregnancy, researchers found women spent 14% of days using cocaine at the beginning of pregnancy, which decreased to 2% by 9 months of pregnancy.⁸⁹ Our study revealed a similar trend, with 80% of women achieving abstinence from cocaine by the 9th month of pregnancy. The affect of time in pregnancy on cocaine use is consistent with studies of other substance use, such as alcohol and tobacco use in pregnancy.³ This finding may be the result of many influences. First, differences between use in the first and second trimesters may represent self-discontinuation of use upon the learning of the pregnancy. Moreover, this finding may reflect knowledge of the negative effects of substance use in

pregnancy, and subsequent motivation to preserve the health of the newborn. Also, cultural and social influences may be at play, as women who are more progressed in pregnancy may feel pressured by negative perceptions of others. Finally, hormonal changes in pregnancy may account for this finding. Progesterone production increases during pregnancy from 40 mgs/24 hours in the luteal phase to 250 mgs/24 hours in late pregnancy. Women also experience massive changes in levels of estrogen, as production of β -estradiol increases from less than 1 mg/24 hours pre-pregnancy to 15-20 mgs/24 hours in late pregnancy. Data from a multitude of preclinical studies suggest that these hormones and their active metabolites affect a wide range of central nervous system functions, and may be implicated in cocaine addiction.⁸⁹ In addition to the downward trend of cocaine use over pregnancy, this study demonstrates that women's use can fluctuate month to month, suggesting that factors other than time in pregnancy play a role in a woman's decision to use cocaine in pregnancy.

Several factors associated with frequency of cocaine use in pregnancy emerged from this study. The most strongly correlated factor with increased cocaine use in pregnancy was severity of use in the 6 months prior to pregnancy. Some researchers contend that frequency of use is a less robust measure of severity, as it does not take into account the impact of drug use on the individual's global functioning and interpersonal relationships.⁷⁷ In our study, this was of less concern, as women were not simply cocaine positive or exposed in their lifetime, but rather were only eligible if they met DSM-IV criteria for abuse or dependence on the MINI International Interview, which incorporates drug-related medical, family, employment, legal and financial problems as part of the assessment.⁹⁰ Frequency of use, therefore, served as a proxy for comparing severity

amongst this subset of cocaine using women. In this study, there was good heterogeneity between different levels of use, as 11 women (22%) reported mild use (<1/week), 17 women (34%) reported moderate use (>1/week, <1/day) and 22 women (44%) reported severe use (>1/day). The levels of baseline use described as moderate and severe were both strongly associated with significantly higher frequencies of cocaine use in pregnancy. This finding suggests that those women who have more frequent use have more severe addiction, and therefore would have greater difficulty achieving abstinence in pregnancy.

Poly-substance use with marijuana was another correlate of heavier cocaine use in pregnancy. This is consistent with the literature, which shows that poly-substance use is associated with more severe addiction; and in particular, cocaine use in pregnancy is strongly correlated with poly-substance use.^{70,80} Additionally, previous reports that have found that marijuana use in adolescence, often considered “gateway” drug use, predicts other illicit drug use in adulthood.²⁴ One Toronto based study of over 1600 women found that of individuals who use cocaine, cannabinoids were used by as high as 46%.²² Patton et. al found that those who used marijuana were nearly five times more likely to use cocaine.²⁴ This finding suggests that women who chose to use, or have access to one illicit drug, are more likely to repeat risky behavior and use other illicit substances. Individuals who use cocaine, in particular, tend to be poly-substance users,⁸⁰ and marijuana is the most used illicit substance in pregnant and non-pregnant adults.¹ Other studies have shown that women who use cocaine in pregnancy tend to have greater alcohol use,⁷⁰ and though alcohol use at any time in pregnancy was prevalent in this study

(56%), it was not a significant correlate of frequency of cocaine use. The conclusion that marijuana use is associated with more frequent cocaine use in pregnancy has important clinical implications, as women may be more likely to report marijuana use than cocaine use, for less fear of legal repercussions and more societal acceptance of marijuana use. Thus screening with self-report may focus on marijuana behaviors to begin to identify women at high risk for cocaine use in pregnancy. Indeed, the Substance Use Risk Profile Pregnancy Scale uses marijuana as a screening tool to identify women at risk of alcohol and drug use in pregnancy, with 100% sensitivity and 64% specificity in low-risk populations.⁹⁵

Later age at onset of first cocaine use was weakly correlated with heavier cocaine use in pregnancy. This finding did not support our hypothesis that earlier age of first cocaine use would be associated with more severe use in pregnancy. Multiple studies have shown that earlier age of onset of substance use, particularly alcohol and tobacco, predict substance abuse later in life.²⁴ With regards to substance use in pregnancy, one nationally representative study found that initiation of smoking at greater than 15 years of age was associated with increased likelihood of abstinence during pregnancy, concluding that the earlier a woman initiates smoking, the more likely it is that she will smoke during pregnancy.⁶⁰ It is possible that onset of cocaine use differs from that of tobacco and alcohol, and therefore results of impact of age of onset may not be generalizable to individuals who use cocaine. Indeed, most studies report that individuals who endorse cocaine use tend to be older than other drug users^{77,78} In a 2013 national survey, median onset of cocaine use was 20.4, compared to 17.8 years for tobacco users and 18 years for

marijuana. Our participants had an average age of onset of cocaine use of 19.9 years (SD= 5.3), reflective of the national average.

Greater social support was associated with mildly heavier cocaine use, which was unexpected, as our hypothesis was that less social support would predict greater cocaine use. Previous studies have found that cocaine using pregnant women tend to have less social support.^{78,80} This study's opposing finding may be due to the nature of the measure we used for social support. The Kendler Social Support Inventory has been used to predict depression in pregnant women, and responses are recorded on scales of frequency of contact with partners, family and friends as well as women's perceived emotional quality of these contacts.⁹¹ It is possible that women who are having more severe cocaine use in pregnancy are reporting greater frequency of contact with family as a result of the consequences of drug-related behaviors, such as financial instability. In other words, support may be higher as a response to heavy-substance using women's greater needs in pregnancy. Whether the interactions are positive or negative cannot be established based on frequency of contact and therefore future studies may consider placing greater weight on the emotional quality of social support when attempting to measure this factor in substance abusing women.

The theory that social support in this population may be a negative factor is supported by results from a case-control study of 200 pregnant women in Detroit, MI, which found that both introduction to alcohol or drugs by a male partner and substance use by family members had a greater effect than other psychosocial risk factors in predicting cocaine use in pregnancy.⁸⁰ In their study, more than one-third of drug users reported that a male

partner had supplied drugs to them at some point. Another study of 240 cocaine and/or opioid dependent women in Baltimore, MD found that similarly over half of women reported that drug use was initiated by a friend (53%), family member (27%) and/or sexual partner (24%).⁷⁸ Although women in their study reported close relationships among family, almost half reported having no close friends and 28% reported spending the majority of their free time alone.⁷⁸ These results taken together suggest that there may be a contextual negative influence of social support in cocaine abusing pregnant women. This knowledge provides a novel implication for screening, as women may be more likely to disclose information on drug use of male partners or other family than self-use.

The lack of significance of comorbid mental illness on frequency of cocaine use was unexpected. Multiple studies have shown that mental health issues co-occur with substance use⁷¹ and may be linked to continued use in pregnancy or relapse to use postpartum.^{61,68,79,96} Our failure to find an impact of mental health may be due to limited power, though there was fair representation of women meeting MINI criteria for major depressive disorder (26%), Anxiety (28%), PTSD (36%), Mania (24%) and Dysthymia (48%). In addition, trauma history was not a significant factor for increased cocaine use in pregnancy for our participants, though mean trauma score was 4.1 (SD=2.4) out of 13 possible points, and some women reported as high as 9 positive responses to trauma events. Again, while previous studies have linked trauma history or abuse with substance use^{75,76}, this study may not have had sufficient power to find this association.

Limitations

There are several limitations of this study. First, as mentioned above, this study had a

small sample size (N=50), which may have led to factors whose correlation was underestimated or deemed insignificant. Pregnant, substance-using women may delay or avoid prenatal care; cocaine-using women may be particularly less likely to endorse use or interact with healthcare for risk of legal and social consequences.^{3,7} It is difficult therefore, to find sizable studies with this population, and more nationally representative studies on factors influencing the decision to use substances, particularly cocaine, are needed.³ Second, this study used data from women who had voluntarily enrolled in a treatment program for cocaine use postpartum, and most were recruited for the study in pregnancy. Therefore these women had demonstrated motivation in pregnancy or postpartum to abstain from cocaine use, so these results may not capture risk factors for cocaine using pregnant women who lack motivation for abstinence and may potentially be the most severe users. Of note, however, 44% of women in this study did report daily cocaine use in the 6 months prior to pregnancy, and at the first month of pregnancy the average reported use of cocaine was weekly use. Third, recruitment was restricted to the New Haven area of Connecticut, so the conclusions we draw here may not be generalizable to all areas of the United States. Studies show that there can be great variability in patterns of use in different regions of countries.³⁷ Lastly, the self-reported use in our study has potential for recall bias, as women were asked to recount cocaine use frequency over multiple months, after having completed their pregnancy. Moreover, urine toxicology screening could not corroborate cocaine use retrospectively. While this is a limitation, it is important to consider that recall as a modality for assessing use in this population may be a strength as well, as women have less incentive to misreport past use for fear of the repercussions of reporting, or fear of negative outcomes of pregnancy.

Clinical Implications

Current screening and identification of substance using women who are pregnant is very poor.⁹⁷ This study identified several factors that can be used by clinicians as correlates of heavier cocaine use in pregnancy, and subsequently serve as a guide for improving screening and directing resources for education of pregnant, cocaine using women. Most screening by providers is done by self-report.⁸⁰ Based on this study's findings, evaluation of a patient's history for baseline cocaine use, concurrent marijuana use, age at onset of cocaine use, and social support can aid in detection of more frequent cocaine use during pregnancy. In particular, positive self-report of greater than weekly cocaine use prior to pregnancy or marijuana use during pregnancy should provide the strongest impetus for further attention. More studies are needed to further understand how social support is assessed for cocaine using pregnant women, as drug involved families or male partners may impede a woman's ability to abstain from cocaine use in pregnancy and may skew our understanding of social support strength for these women. In addition to implications for screening, understanding risk factors for drug use in pregnancy can help in designing more effective prevention as well as treatment strategies. To that end, this study adds to our understanding of risk factors for cocaine use in pregnancy, and larger, more nationally representative studies are needed in the future to further this understanding.

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