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Barbara A. McGee
Yale University

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The purpose of the present study was to prospectively examine the following hypothesis: Cocaine use among pregnant women maintained on methadone increases the duration and the severity of the neonatal abstinence syndrome (NAS) among their infants. A group of 23 infants born to mothers participating in a methadone maintenance program were followed for severity of NAS after poly-drug exposure *in utero*. Severity of withdrawal was indexed by infant length of stay in the hospital, duration of treatment with medication, first and maximum symptom scores, and the dosages of withdrawal medications used. During pregnancy, information was gathered on maternal daily methadone dose, urine toxicology, pregnancy complications, and medication use. Fourteen (61%) of the mothers in the sample had positive urine screens for cocaine, and five (22%) took benzodiazepines regularly during pregnancy. Infants exposed to both cocaine and methadone trended toward a shorter duration of therapy, however, the differences were not found to be statistically significant ($F = 1.54$, $p = .23$). There was a positive correlation between maternal methadone dose and the number of days infants spent on the highest doses of withdrawal medication ($r = .53$, $p \leq .01$). In addition, benzodiazepine exposure significantly contributed to longer infant hospital stays ($F = 8.3$, $p < .01$), and duration of medication treatment ($F = 10.37$, $p < .01$). These findings suggest that the effect of cocaine on withdrawal from methadone in infants is small, having either no contributory effect or only a mild degree of shortening of the duration of withdrawal symptoms.

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TABLE OF CONTENTS

INTRODUCTION

Substance abuse in pregnancy

More than 100,000 babies born in the United States annually are believed to have been exposed to cocaine or other drugs during the critical period of fetal brain development.[1] The National Institute on Drug Abuse reports 70 to 90% of Americans between the ages of 15 to 40 years have used mood-altering chemicals, approximately half of whom are women with reproductive potential.[2] Among women in this group, approximately 60% drink alcohol, 32% smoke nicotine cigarettes, and 11% use marijuana. Some reports suggest a leveling off of overall cocaine use in this country over the last five years.[3] However, young women continue to be the fastest growing group of cocaine users, with some cities reporting a 12 to 15% increase in cocaine use among women since 1991. In a population of women presenting for prenatal care, screening a single urine sample for alcohol, cannabinoids, cocaine, and opiates reveals positive urine toxicology results in 3 to 50% of cases, depending on the methods and populations studied.[4-6]

A 1988 study,[2] conducted by the National Association of Perinatal Addiction Research and Education, and involving approximately 155,000 pregnancies annually from 36 hospitals around the country, found that 11% of the mothers used at least one of the following: heroin, methadone, marijuana, PCP, amphetamines, and most commonly cocaine. A later study of infants born to substance abusing mothers in New York City revealed the changing patterns of drug exposure through the 1980's.[7] Initially, heroin and

methadone use during pregnancy predominated. As crack became more readily available, the trend began to shift toward increasing cocaine use in pregnancy, with frequency of cocaine use being reported on birth certificates 2.3 times more frequently than heroin and methadone combined. Frequently, more than one drug is being abused during pregnancy. Among women maintained on methadone for opiate addiction, concomitant, regular use of cocaine or crack has been reported in 20 to 60%.[8, 9]

The increase in cocaine use among women of reproductive age has caused concern about the potential maternal and fetal effects of illicit drug abuse during pregnancy. Pregnancy in women who use illegal drugs or alcohol is, by definition, a high risk. In untreated women who use cocaine during pregnancy, serious complications have been reported, such as maternal deaths, myocardial infarction, cerebrovascular accidents, and abruptio placentae.[10-18] A correlation exists between substance abuse in pregnancy and a higher exposure to sexually transmitted diseases, systemic infections including HIV, poor nutrition, decreased use of health services, and indiscriminate sexual activity.[12, 13, 19 -21] These factors, as well as the chaotic lifestyle that accompanies substance abuse,[22] creates a high-risk environment for fetal development, warranting concern about the outcome of infants exposed to drugs *in utero*.

Neonatal abstinence syndrome

One clear outcome of substance abuse in pregnancy is exhibited by the neonatal withdrawal syndrome experienced by infants born to opiate-addicted mothers. Newborns who have been exposed prenatally to heroin or methadone are born passively addicted to the drug and exhibit withdrawal symptoms in the first days to weeks after delivery.[23-25] Heroin and methadone are easily transferred across the placenta, and have been found to accumulate in fetal tissues and fluids when exposure occurs during gestation.[26, 27] Neonatal Abstinence Syndrome (NAS) results when the placental transfer of opiates to the infant is disrupted by delivery. The majority of infants born to opiate-addicted women experience NAS,[28] which is characterized by signs and symptoms of central nervous system hyperirritability, gastrointestinal dysfunction, respiratory distress, poor sucking reflex, tremors, hypertonicity, and high pitched crying (Figure 1). The majority of symptoms appear within 72 hours of delivery.[29] Several types of clinical courses have been described in the literature on NAS.[29] Withdrawal has been noted to be mild and brief, be delayed in onset, have a step-wise increase in severity, or have a biphasic course. More severe withdrawal tends to occur in infants whose mothers have taken large amounts of drugs for a long time.[30, 31] In general, the closer to delivery a mother takes heroin, the greater the delay in onset of withdrawal and the more severe the symptoms in her baby. Duration of symptoms can extend from six days to twelve weeks depending on the extent of drug exposure, as well as concomitant medical problems of the infant. During the later weeks of withdrawal,

infants may have hyperphagia, increased sucking, sweating, irregular sleep patterns, loose stools, and poor tolerance to holding or to abrupt changes of position and space.[29]

The severity of withdrawal in an infant exposed to opiates *in utero* is generally monitored by following specific symptoms with a standardized scoring system. An early scoring system was proposed by Lipsitz[32] to quantitate the clinical symptoms of abstinence. The degree of tremor, irritability, and gastrointestinal symptoms were scored from zero to three, based on observer judgement. The presence or absence of tachypnea, sneezing, yawning, vomiting, and fever were noted and scored as either zero or one. A cumulative withdrawal score was then calculated and the assessment could be repeated at a standard frequency during the infant hospital stay. In this way, infants were compared to each other and the progression of withdrawal severity was monitored in individual infants. A more detailed system of scoring was developed and standardized by Finnegan,[33] which serves as the basis for most withdrawal measuring systems currently in use at pediatric hospitals in this country (Figure 2). The Finnegan scale measures 21 signs of withdrawal and allows scores to be obtained at regular intervals during a twenty-four hour period. The scores obtained serve as a means for communication regarding withdrawal severity within research studies, as well as a clinical measure utilized when making treatment decisions.

When abstinence scores for an infant exposed to opiates reach a particular threshold, pharmacotherapy may be used to alleviate withdrawal symptoms. Treatment is usually initiated within the first days of life. Symptoms are brought under control and the

infant is gradually withdrawn from the medication. Medication for withdrawal has typically consisted of either opiate substitutes,[31, 34, 35] or nonspecific depressants such as phenobarbital,[36] diazepam,[31] and chlorpromazine.[34, 36, 37] Paregoric, a tincture of opium, is generally considered the treatment of choice for NAS in this country.[38] Phenobarbital is often added or used as a second line drug for symptom control. Although morbidity associated with NAS is decreased with treatment, therapeutic management may require a prolonged hospital stay.

Methadone maintenance during pregnancy

It has been reported that entry into a methadone maintenance program serves to encourage better participation in prenatal care and provide a more stable environment for pregnant opiate addicts.[39, 40] Methadone is a long-acting synthetic opioid that can be taken by mouth, thereby reducing the risk of infection acquired by the sharing of contaminated needles or syringes as in heroin use. Methadone blocks the euphoria produced by heroin and blunts the appetite for repeated administration of opiates. A free and regular supply of methadone from an established clinic also decreases the likelihood that patients will engage in prostitution or criminal activities which are detrimental to their physical and mental well-being. Also, it has been argued that with steady methadone maintenance the fetus would not suffer from fluctuating levels of opiates and therefore the incidence of intrauterine withdrawal would be less.[40] It has been shown that methadone maintenance, in conjunction

with adequate prenatal care, significantly reduces the incidence of medical and obstetrical complications and prematurity.[41] Studies have also consistently found differential effects of heroin and methadone on birth weight, with higher birth weight infants born to women maintained on methadone.[24, 42]

It has been suggested that methadone produces more severe withdrawal manifestations than heroin.[34, 35] However, measurement of heroin intake is rarely possible, and most studies have been laden with the dilemma of concurrent poly-drug use. The severity of the neonatal abstinence syndrome may largely be determined by total intrauterine drug exposure.[43, 44] Many studies have debated the relationship of total maternal methadone intake, and by extension total fetal exposure, to the severity of subsequent neonatal withdrawal symptoms.[38, 45, 46] Doberczak et al,[46] in 1993, studied a group of 21 methadone-dependent women and their infants to define the relationship between neonatal opiate withdrawal and maternal methadone dose. They found that higher initial plasma methadone levels were associated with more rapid declines of drug levels in methadone-exposed neonates. The more rapid rate of decrease in serum methadone levels after birth correlated significantly with acuity of central nervous system withdrawal signs observed in their sample of infants. These results are consistent with animal studies which have shown that methadone accumulates in the non-human primate brain during gestation, resulting in significantly higher brain levels compared with fetal plasma levels.[47, 48] In addition, intrauterine exposure of the fetal brain to opiates promotes regional

development of specific opiate receptors and suppresses neurotransmitter formation and function.[26, 49] Thus, a more rapid decline in methadone levels in the first hours after delivery would produce a rapid shift of drug out of brain tissue, leading to increased availability of specific opiate receptors as well as rapid replenishment of neurotransmitters. In the presence of increased receptor sites, this replenishment of neurotransmitters would produce neuronal excitability, clinically manifested as central nervous system signs of withdrawal such as irritability, tremors, hyperreflexia, and possibly seizures.[46]

With the potential for a more severe withdrawal course in infants exposed to methadone, the suggestion has been made that lowering dosages of methadone late in pregnancy may ameliorate neonatal opiate withdrawal, and thereby benefit the mother and infant.[46, 50] However, methadone regimens are generally individualized to determine the dose that will prevent the development of withdrawal symptoms in a pregnant woman. If the reduction of methadone dosage is attempted, there is always the fear of fetal instability from withdrawal,[51] or the possibility of fetal death.[52] In addition, dosage reduction carries the risk of maternal discomfort and self-medication with street drugs, thus increasing neonatal morbidity and decreasing the overall value of methadone maintenance to the health of the woman.

Outcome after fetal opiate exposure

Maternal opiate addiction is associated with increased perinatal morbidity and mortality.[53] Problems associated with heroin use during pregnancy include first-trimester spontaneous abortion, premature delivery, meconium staining, and maternal and neonatal infections.[54] In general, studies that have compared birth outcomes of opiate exposed infants and non-drug exposed infants have consistently found opiate exposed infants to have lower birth weights than comparison infants.[41, 42, 55, 56] Although the birth weights of methadone exposed infants are higher than those of heroin addicts, they are still less than nonaddicted controls.[57] In addition, numerous studies have now replicated the finding that prenatal opiate exposure reduces head circumference.[41, 42, 58] Similar findings in animal models that control for exposure to other drugs such as alcohol or tobacco, and for poor maternal health support the finding of an effect of opiates on fetal growth.[59] Prenatal exposure to opiates may contribute significantly to an increased incidence of sudden infant death syndrome (SIDS)[7]. In some studies, the incidence of SIDS is eight times that reported for non-opiate-exposed infants.[60-62]

Past the neonatal period, a number of studies have documented small, and not usually statistically significant, delays in the acquisition of developmental skills as measured by the Bayley Scales of Infant Development.[56, 58, 62, 63] However, much more consistent across studies have been the findings of persistent problems in poor motor coordination, high activity level, and poor attention among opiate-exposed infants in the first year of

life.[64, 65] Similarly, opiate-exposed school-age children show higher activity levels, are often impulsive with poor self-control, show poor motor coordination, and have more difficulty with tasks requiring focused attention.[66, 67] Maternal poly-drug use has been a major confounding factor in studies investigating the effects of prenatal exposure to illicit drugs. As well, the effect of the care-taking environment for children in substance-abusing families is undoubtedly a significant factor in developmental outcome, and has not consistently been controlled for in scientific studies.

Cocaine use in pregnancy

Cocaine is one of the most frequently used illicit drugs, with national trends indicating that cocaine, and in particular crack, continues to dominate the drug scene.[3] Although overall use of cocaine appears to have leveled off in most cities in the United States, some indicators point to an increase in the number of female cocaine users.[3] Crack remains the most popular form of cocaine, presumably due to the ready availability and low cost of the drug. In Philadelphia, a large rock, or boulder, sells for about five dollars. In Seattle, little bits of crack called kibbles sell for one dollar.[3] With crack so easily available, the incidence of cocaine use in pregnancy has been reported at 10 to 19%.[4, 68-70]

Cocaine is a powerful stimulant drug that in its freebased form, crack, can be smoked to induce short periods of intense euphoric feelings, during which energy and self-esteem are enhanced and anxiety are decreased.[71] However, within hours of use,

cocaine's rebound effects result in anxiety, exhaustion, and depressive feelings. The dependent person takes cocaine repeatedly to avoid the crash rebound effects. Chronic use can result in psychologic and physical symptoms, including paranoid and mood disorders, weight loss, and decline in judgment.[72] In adults, the acute and chronic effects of cocaine are demonstrated through significant alterations of central nervous system function.[11, 73]

Due to cocaine's low molecular weight and its water and lipid solubility, it readily crosses the placenta and the fetal blood brain barrier.[74] Plasma cholinesterase, which inactivates cocaine, is relatively deficient in the mother and fetus, possible resulting in a greater time of exposure to the active drug. One adverse effect of cocaine on the fetus is uterine vessel vasoconstriction with reduced uterine blood flow and oxygen transfer.[75] Experiments in animals have also suggested a teratogenic effect,[76] and permanent degeneration of nerve terminals in adult animals.[77, 78] Thus, cocaine may have direct neurotoxicity or indirect effects via vasoconstriction on the developing nervous system.

Cocaine and central nervous system development

The primary central nervous system (CNS) action of cocaine occurs through the monoaminergic neurotransmitter systems including dopamine, norepinephrine, and serotonin (5-HT). Cocaine blocks the reuptake of dopamine, norepinephrine, and 5-HT by the presynaptic neuron, a process that is primarily responsible for inactivation of

neurotransmitters.[79] Blocking reuptake leaves more monoamine neurotransmitters available within the synaptic space and results in enhanced activity of these agents in the CNS. The various dopamine-rich areas of the brain are involved in a number of basic neuropsychological functions including arousal and attentional modulation, the regulation of anxiety and other emotional states, and the reinforcing properties basic to stimulant addiction in adults. In fetal brain development, monoaminergic neurotransmitters are critical for the definition of brain structure and neuronal formation through their effects on cell proliferation, neural outgrowth, and synaptogenesis.[80, 81] Alterations in developing monoaminergic systems may lead to mistimed neurogenesis, and resultant alterations in synaptic connections.[82] In addition, prenatally cocaine-exposed infants might be expected to be compromised specifically in areas such as reactivity, capacity to modulate levels of arousal in response to stimulation, and attentional regulation.[83]

Perinatal complications associated with cocaine use

Numerous reports have described significant obstetric and neonatal complications associated with maternal cocaine use during pregnancy. Among the most compelling findings are consistent descriptions of increased rates of spontaneous abortions, abruptio placentae, and meconium-stained amniotic fluid.[17, 28, 68, 84] Intrauterine growth retardation has been found in all studies of reasonable size in which cocaine-exposed neonates were compared with non-drug-exposed newborns.[18, 28, 68, 85, 86]

Increased rates of prematurity and lowered gestational age in cocaine-exposed pregnancies have been found,[17, 86-88] suggesting that prematurity or its complications may be indirect mechanisms by which cocaine's neurodevelopmental effects are expressed. Alternatively, premature birth may be a marker for mothers with greater dependency on drugs, a heavier use of drugs, or significant socioeconomic disadvantages.[72] Marijuana use, alcohol use, and cigarette use have also been shown to be significant independent or interactive contributors to reduced fetal health in samples of poor, urban, minority pregnant women.[18, 84] Some available studies have had methodologic problems that prevent clear attribution of the poor medical outcomes of cocaine-exposed pregnancies to cocaine use alone. These problems include poorly defined or highly selective samples, misidentification of subjects, lack of appropriate comparison groups, and retrospective sampling.[89]

Infant outcome after prenatal cocaine exposure

Exposure to cocaine and other drugs places infants at risk for developmental dysfunctions. For example, infant neurological examinations soon after birth have documented increased tremors, irritability, and hypertonicity in infants exposed to cocaine.[31, 90, 91] The Brazelton Neonatal Behavioral Assessment Scale (NBAS) has been the most consistently used assessment of newborn neurobehavioral characteristics,[92-94] and it is frequently the outcome measure of choice in studies of the neurobehavioral effects of prenatal drug or potential teratogen exposure.[17, 65, 95] In three studies to date, reporting on

cocaine exposure without concomitant opiate use, and with or without concomitant alcohol use, findings have been inconsistent.[1, 84, 95] Chasnoff and colleagues[1] found impairments of orientation, motor, and state regulatory behaviors on the NBAS. In contrast, Coles et al[84] reported that NBAS scores for all newborns fell within a clinically normal range regardless of cocaine or alcohol exposure. Although significant differences emerged between groups for autonomic regulation and for abnormal reflexes, the less optimal performance was not consistently more frequent among the cocaine-exposed group only, and no clear patterns of effect emerged. Finally, Eisen and colleagues,[95] studying neonates who were urine screen positive only for cocaine at birth and whose mothers denied opiate use, found significant differences in habituation performance as assessed by the NBAS. Habituation is involved with attention and information processing and perhaps learning in infants.[96] Depressed habituation performance on the NBAS in infants exposed to cocaine would suggest a link between the effects of cocaine on the developing brain and neurobehavioral outcome.

In early reports regarding the long-term developmental outcome of infants exposed to cocaine as well as combinations of heroin, methadone, and marijuana, cocaine exposure was predictively linked to moderate to severe developmental delays across diverse developmental domains.[97] However, subsequent studies have reported mild to no impairments in overall developmental functioning in cocaine-exposed children compared to non-exposed groups.[98, 99] The findings from a 3-year outcome study by Azuma and Chasnoff[100] indicated that prenatal substance exposure had a significant effect on cognitive

abilities as measured by the Stanford-Binet scale. It was acknowledged, however, that the nature of the effect on intellectual outcome is complex, due to the influences of home environment, child behavior, and head circumference which confound studies with this group of children. Therefore, other causal models for attributing poor Stanford-Binet scores to a drug exposed population of children could not be ruled out. Therefore, such factors as socioeconomic status, behavioral characteristics, and quality of the home environment continue to complicate the ability to draw conclusions from studies of drug exposure in children.

Interactive effect of cocaine and opiates

Infants with combined exposure to narcotics and cocaine have been shown to have a worse perinatal outcome when compared to other drug exposures in pregnancy.[88] Among women maintained on methadone for opiate addiction, concomitant, regular cocaine or crack use has been reported in 20 to 60%.[8, 9] Combinations of opiate and cocaine use during pregnancy raise concerns about a potentially interactive effect on the withdrawal syndrome, and exacerbation of adverse perinatal outcomes. In a phenomenon called the "kindling effect," repeated doses of cocaine result in progressively increasing central nervous system sensitivity, thereby increasing reactivity to the central effects of other drugs.[101, 102] Pinel and Van Ott reported that repeated cocaine administration in animals leads to more severe withdrawal from a second drug such as heroin and amphetamines.[103]

There are conflicting reports published regarding the interactive effect between cocaine and opiates. In adult opiate addicts applying for methadone maintenance, it has been reported that cocaine significantly lowered levels of naloxone-precipitated withdrawal.[104] However, adult patients in another study reported that cocaine use precipitated symptoms similar to opiate withdrawal.[105] For human infants potentially interactive effects between cocaine and opiates on neonatal withdrawal have been reported for infants exposed to heroin and cocaine prenatally. Fulroth and colleagues studied the withdrawal course of 86 infants after maternal heroin use.[106] Seventeen infants were exposed to both heroin and cocaine, and 14 to heroin alone. Using the Finnegan scoring system, infants were treated for withdrawal when scores were greater than 12 over an eight hour period in the first five days of life. In their population of patients a significant difference was found between the withdrawal course of heroin-only infants and those exposed to both opiates and cocaine. They found that 21% of the infants exposed only to heroin required treatment for withdrawal, compared with 47% of the infants exposed to both heroin and cocaine. The conclusion drawn from this data was that cocaine had a synergistic effect on the withdrawal syndrome seen after *in utero* heroin exposure.

In contrast, in the retrospective study by Mayes and Carroll,[107] suggested that the effect of cocaine, if any, on neonatal opiate withdrawal was most notable in the initial phase of withdrawal. In their study, 68 women and infant pairs were analyzed for measures of withdrawal severity. In that cohort, cocaine exposure resulted in significantly higher first

withdrawal scores, but there were no significant differences in the amount of time on withdrawal medication or the maximum doses of paregoric required for withdrawal treatment.

Another study to look at the specific question of cocaine effects on opiate withdrawal was performed by Ryan et al.[108] In that study, 50 methadone-exposed infants were compared with 50 methadone and cocaine-exposed infants, using parameters of neonatal morbidity and mortality, as well as abstinence scoring immediately after birth to determine outcome. The most significant findings included lower birth weight, length, and head circumferences for cocaine-exposed infants when compared with a group of infants not exposed to cocaine or methadone. In addition, their data suggested a higher rate of fetal loss and infant mortality after cocaine exposure in pregnancy. To determine the effect of cocaine exposure on neonatal abstinence severity in that population, Ryan et al compared individual symptom frequency, as scored on the Finnegan scale. It was noted that episodes of abstinence symptoms occurred less frequently in infants exposed to a combination of cocaine and methadone in 19 of the 21 symptom categories. This trend was not found to be statistically significant, thus the authors concluded that cocaine exposure had no effect on the severity of withdrawal in opiate-exposed infants.

Finally, Doberczak and colleagues examined the effects of gestational age on the neonatal abstinence syndrome, with and without concomitant cocaine exposure.[109] In this cohort of methadone-maintained mothers, severity of abstinence symptoms correlated with

maternal methadone dosage, but was not influenced by maternal multiple drug use. Therefore, with the results of current research available, the question of how cocaine affects the severity of neonatal withdrawal from opiates remains inadequately answered. It could be hypothesized, based on a review of the literature, that cocaine exposure would exacerbate the central nervous system irritability that is a central aspect of the neonatal abstinence syndrome. Theoretically, the direct stimulant effects of cocaine would mimic opiate withdrawal symptomatology early on in the neonatal course, causing earlier and more frequent need for treatment of withdrawal in dually exposed infants. In addition, the direct effects of cocaine on neurodevelopment of the fetus could potentially cause an anatomic or neurophysiologic basis for a longer-term altered neurologic status in cocaine-exposed infants. This altered baseline of functioning could affect the appearance of neonatal withdrawal symptoms, such that the neonatal abstinence syndrome is essentially changed in these infants. Delineating such questions may serve to improve the treatment and understanding of long-term outcome in infants exposed to narcotics and cocaine concomitantly *in utero*.

PURPOSE

The purpose of the present study was to prospectively examine the following hypothesis: Cocaine use among pregnant women maintained on methadone increases the duration and the severity of the withdrawal syndrome among their infants. The severity of withdrawal was indexed by infant length of stay in the hospital, duration of treatment with medication, first withdrawal scores, and the dosages of withdrawal medications used.

METHODS

Study sample

The study sample consisted of pregnant narcotic-addicted women maintained on methadone, and their infants, born at Yale New Haven Hospital (YNHH). Women were recruited to participate in the study through a methadone maintenance program for opiate addicted individuals offered through the Substance Abuse Treatment Unit of the Yale University School of Medicine Department of Psychiatry. Women eligible for the study were participants of the methadone program who had delivered a child while on methadone, during a period of 23 months (October, 1995 - August, 1997). During this period, 24 infants were born at YNHH to methadone-maintained women.

All of the pregnant women in the study sample received their daily methadone dose at the Substance Abuse Treatment Unit. Urine screens for elicit drugs (cocaine, heroin, methamphetamine, benzodiazepines, and barbiturates) were performed routinely and randomly during the mothers' methadone maintenance course. Women participated in regular group counseling sessions for pregnant substance users as a part of the methadone maintenance program, with direct regular contact with a trained substance abuse treatment nurse.

Recruitment to the study was performed through the group counseling sessions, with study coordinators obtaining consent from the mothers during their pregnancy to have access to the drug treatment records of the mothers, as well as follow the infant in the

hospital for narcotic withdrawal. Informed consent for participation in the study was obtained by one of the researchers (B.T.). All pregnancy, drug history, and infant information was gathered with the maintenance of strict confidentiality, as approved by the institutional review committee of the Yale University School of Medicine.

Study protocol

During pregnancy, information was gathered on daily methadone dose, urine toxicology, pregnancy complications, and medication use. All infants were delivered at Yale New Haven Hospital, and mother and infants charts were reviewed for prenatal and delivery information at the time of hospitalization. Infants were routinely admitted to the Special Care Nursery and observed for withdrawal symptoms within the first 48 hours of life. Each infant was transferred to the Children's Clinical Research Center within 24 hours of beginning medication for narcotic withdrawal when it was determined that there were no other complications needing intensive care unit observation. Gestational age was estimated by attending pediatricians in the newborn nursery using the Ballard criteria.[110]

Abstinence scoring

Drug withdrawal assessment was performed by nursing staff in the CCRC trained to use the abstinence scoring system of Finnegan,[33] modified (see Figure 2), which measures 21 signs of withdrawal including increased tone, tremulousness, tachypnea, decreased

sleep, and feeding disturbances. Scores were assigned every eight hours, and the initial assessment was made in the first eight hours after birth. Nursing staff performing the assessments were blinded to the drug history of the mother, with information only that the mother had taken methadone during pregnancy. Treatment was routinely begun for withdrawal when withdrawal scores exceeded 12 for two consecutive scoring periods. The first drug prescribed for withdrawal symptoms was paregoric in all infants. If the infant remained symptomatic, phenobarbital was added. In one infant, no medications were used to treat narcotic withdrawal specifically. An increase or decrease in dosage of withdrawal medication was determined by the infant's withdrawal symptoms. Infants were always weaned off medication before discharge from the hospital and were not transferred to another institution or released home until they were symptom free.

Information regarding the infant's withdrawal course was recorded on a daily basis, focusing on the following parameters: individual shift withdrawal scores; total daily withdrawal score; medication type, dose, and frequency of administration; weight gain; feeding type and amount; and frequency of perinatal problems such as jaundice, respiratory distress, or dysmorphic features.

Statistical analysis

We compared groups with a one-way ANOVA test, and Pearson's chi-square. $P < .05$ was considered significant. All data are represented as mean (Standard Deviation).

RESULTS

Twenty-four women who were receiving methadone during pregnancy through SATU, and who delivered infants at YNHH were identified in this study period. One mother refused access to her drug history information as a part of the study, and thus data on the infant were not included in the present analysis. In the final analysis, data from 23 mother and infant sets were used.

Table 1 shows the demographic characteristics of the sample. Women in this sample were usually in their mid-twenties (mean 26.9, S.D. 5.4), and had had multiple previous pregnancies (mean 3.7, S.D. 2.0). The sample was predominantly caucasian (56.5%) with 26.1% of Hispanic ethnicity and 17.4% African-American. The HIV status was known for 17 women, one of whom was positive. Of the women for whom hepatitis B and C test results were available (n = 20), three were positive (13%), with one positive for hepatitis B and C, and two for hepatitis C only. Fifteen of the 23 mothers presented to the methadone clinic at some point in their pregnancy, and the remaining eight were already in the methadone program when they became pregnant. Mothers had been receiving methadone for a mean of 26.7 weeks (SD 12.3) at the time of delivery.

Maternal urine toxicology

Fourteen mothers (60.9%) who were receiving methadone also reported regular use of cocaine or had positive urine screens for cocaine during pregnancy. When mothers who

used cocaine during their pregnancy in addition to methadone were compared to mothers maintained on methadone who did not use cocaine, there were no differences in maternal age, ethnicity, number of pregnancies, or the frequency of tobacco use. There was no difference in methadone dose at the time of delivery between the two groups. There seemed to be a trend toward later enrollment in the methadone program for mothers who also used cocaine during pregnancy, however, the difference did not reach statistical significance. The mean gestational age at enrollment for non-cocaine exposed of 8.2 weeks (SD 8.4) and for cocaine-exposed of 12.0 weeks (SD 11.69), F=.7006, p=.4120. Other drug use in pregnancy was similar between the two groups, with no positive urine screens for amphetamines, and near equal numbers in each group using benzodiazepines. Of those who used cocaine during pregnancy, three (21.4%) also had positive urine screens for benzodiazepines. Of the nine mothers who did not use cocaine while maintained on methadone, two (22.2%) had positive urine screens for benzodiazepines throughout pregnancy.

Perinatal outcome

There were seven male and sixteen female infants. As indicated in table 2, the mean gestational age for the overall sample was 37.5 weeks by Ballard criteria (S.D. 3.7) with a range of 27 to 41 weeks. The mean birth weight for the overall group was 2646 g (S.D. 692) and four infants were small for gestational age. The most frequent perinatal

complication was low birth weight, with 39.1% of the overall sample born at under 2500 grams. In addition, 34.8% of the group of 23 infants were delivered at a gestational age of less than 37 weeks. One infant was born at 27 weeks, with a birthweight of 830 grams. There was a trend toward the cocaine-using women to have more frequent preterm labor, and a greater number of perinatal problems, however the differences were not found to be statistically significant. Fourteen infants (60.9%) had additional complications during hospitalization. Of these, the most common was hyperbilirubinemia (21.7%), with two infants with positive Coombs results. Three infants (13%) had a hospital course that was complicated by infection. Similarly, three infants (13%) were observed to have at least one episode of apnea while in the hospital. Two infants were diagnosed with a cardiac arrhythmia, and one infant was found to have a heart murmur, macrocephaly, and dysmorphic features. One infant tested HIV positive during the first month of life.

The infants withdrawing from methadone spent an average of 34.3 days (S.D. 18.7; range 13-85) in the hospital. Infants were treated with medication for withdrawal for an average of 27.6 days (S.D. 19.7; range 0-81). The majority of infants showed withdrawal symptoms within the first 24 hours (mean 13.2 hours, S.D. 10.8), and were started on medication for withdrawal at an average of 43.3 hours of age (S.D. 56.2; range 4-264). Paregoric was the first medication used in all infants, and phenobarbital was added to paregoric for treatment of continued withdrawal symptoms in three cases. One infant required no medication for withdrawal.

Withdrawal course by cocaine exposure status

Several parameters were used to compare the withdrawal course of infants whose mothers used cocaine in addition to methadone (n=14) and those who did not (n=9). The severity of the withdrawal course was measured by the first and maximum withdrawal symptom scores, the maximum dose of paregoric required, the length of stay in the hospital, the total number of days on withdrawal medication, and the addition of phenobarbital to paregoric for adequate withdrawal treatment. Complications which affected the hospital course of the infant, such as prematurity or apnea, were noted and compared between the two groups as a measure of poor perinatal outcome.

When infants exposed to cocaine plus methadone were compared to those whose mothers did not use cocaine, the cocaine exposed group trended toward a shorter withdrawal course, with trends toward a shorter duration of medication treatment, shorter length of stay, and fewer number of days on the highest doses of paregoric. However, the statistical differences were not significant to show a strong association between cocaine exposure and a shorter withdrawal course. Cocaine-exposed infants required medication for withdrawal symptoms at a later age than the methadone-only infants (53.0 versus 28.2 hours of life), but the difference did not reach statistical significance. Also, cocaine-exposed infants tended to require a fewer number of days at the highest doses of paregoric (3.9 versus 7.9 days), a difference that was not statistically significant. There were no differences in first withdrawal scores, age at first withdrawal symptoms, highest dose of

paregoric required, duration of medication treatment, or length of stay in the hospital between the cocaine exposed and cocaine non-exposed groups.

Three infants required the addition of phenobarbital to paregoric for the treatment of more severe withdrawal symptoms. Two infants who received phenobarbital were exposed to cocaine, and one was exposed only to methadone. One infant who was not exposed to cocaine prenatally required no treatment with paregoric for withdrawal, and one who was exposed to cocaine in addition to methadone required only two days of medication treatment for withdrawal. The number of infants experiencing complications while in the hospital was six (66.7%) for the cocaine-exposed and eight (57.1%) for the group not exposed to cocaine, a difference that did not reach statistical significance. Those who were born at less than 2500 grams were approximately evenly distributed between groups, with four (44.4%) in the group not exposed to cocaine and five (35.7%) in the cocaine-exposed group of infants. In addition, one infant was born at under 30 weeks, and was a part of the cocaine-exposed cohort. However, there was no difference overall in gestational age between the two groups (37.9 weeks and 37.3 weeks). Of the four infants who were classified as small for gestational age, three were in the cocaine negative group and one was cocaine-exposed.

Effect of maternal methadone dose

In the present analysis, cocaine exposure was not significantly correlated with specific measures for severity of narcotic withdrawal, and only showed trends toward a less prolonged course of treatment. However, maternal methadone dose at the time of delivery did seem to be a significant contributor to the quality of the infant's withdrawal course. Maternal methadone dose was positively correlated with the number of days that infants spent at the highest doses of paregoric [correlation coefficient (r) = .53, $p \leq .01$]. In addition, there was a fair correlation between methadone dose at the time of delivery and length of stay of the infant in the hospital (r=.37, $p \leq .08$), and the highest dose of paregoric required for treatment of withdrawal (r=.23, $p \leq .30$). There was a negative correlation at a fair level between maternal methadone dose and the age of the infant at the time of first withdrawal symptoms (r= -.37, $p \leq .09$), and with age at the time of first medication treatment (r= -.24, $p \leq .30$). The infants (n=3) who required the addition of phenobarbital to paregoric for adequate treatment of withdrawal had been exposed to methadone at an average daily dose of 90 mg at the time of delivery, whereas the overall group mean daily dose was 77.8 mg.

Effect of benzodiazepine exposure

During the data collection phase of the study, it became evident that a number of infants were consistently exposed to benzodiazepines in utero. This drug exposure

information was incorporated into a separate analysis to study the effect of benzodiazepine exposure on infant withdrawal course. We compared infants who were exposed to benzodiazepines in addition to methadone to the infants who were exposed to methadone without benzodiazepines. The cocaine exposure status was not used as a factor in this portion of the analysis. When mothers who used benzodiazepines were compared to mothers who did not use benzodiazepines during pregnancy (Table 4), it was found that benzodiazepine users were maintained on a higher dose of methadone and had a significantly higher daily dose of methadone at the time of delivery ($F=9.92$, $p = .005$). The infants of benzodiazepine-using mothers had significantly longer hospital stays ($F=8.29$, $p < .01$), longer duration of withdrawal medication treatment ($F=10.37$, $p < .01$), and spent more days at the highest doses of paregoric ($F=5.36$, $p < .05$). There were no significant differences in first withdrawal score, age at first withdrawal score, age at first medication treatment, or the highest dose of paregoric required to treat withdrawal symptoms. The number of complications experienced while in the hospital was equal for infants exposed to benzodiazepines and those who were not exposed to benzodiazepines (.94 and 1.20 respectively). The addition of phenobarbital was required for the treatment of withdrawal in one infant (5.6%) not exposed to benzodiazepines, and two infants (40%) with benzodiazepine exposure.

DISCUSSION

Relationship of cocaine exposure to severity of withdrawal

In the present study, the relationship between cocaine exposure and the severity of the neonatal abstinence syndrome was investigated in a prospective manner. The primary hypothesis of this study was that a combination of methadone and cocaine use during pregnancy contributed to a more prolonged and potentially more severe neonatal withdrawal course than would be expected with exposure to methadone alone. This hypothesis was not proven by the findings in this prospective cohort. On the contrary, there is a suggestion that in the group exposed to cocaine in addition to methadone there was a trend toward a shorter and less severe withdrawal course. Although not found to be statistically significant, the data suggested that infants who were exposed to cocaine had a shorter duration of treatment with withdrawal medications, shorter length of stay, and fewer number of days on the highest doses of paregoric. These findings suggest that the effect of cocaine on withdrawal from methadone in infants is small, and either has no contributory effect to the overall severity of narcotic withdrawal, or accounts for only a mild degree of shortening in the duration of withdrawal symptoms.

The results of this study are in contrast, somewhat, to the retrospective view performed by Mayes and Carroll,[107] looking at a cohort of women who received methadone during pregnancy through the same treatment program as women in the present study. Data from 68 women and infant pairs were collected, and analyzed for measures of

withdrawal severity which parallel the present study. In that cohort, cocaine exposure resulted in significantly higher first withdrawal scores, but there were no significant differences in the amount of time on withdrawal medication or the maximum required doses of paregoric. Those results suggested that the effect of cocaine, if any, on neonatal opiate withdrawal was most notable in the initial phase of withdrawal.

Another study with results conflicting with the present findings was performed by Fulroth et al.[106] They studied the withdrawal course of 86 infants, 17 of whom had positive urine screens for both heroin and cocaine, and 14 for heroin only at the time of birth. They found that 21% of the infants exposed only to heroin required withdrawal treatment, compared with 47% of infants exposed to both heroin and cocaine. The conclusion drawn from this data was that cocaine had a synergistic effect on the withdrawal syndrome seen after *in utero* heroin exposure.

However, a third study, performed by Ryan et al,[108] found that cocaine exposure may have lessened or had no effect on the severity of withdrawal in opiate-exposed infants. The most significant findings included lower birth weight, length, and head circumferences for cocaine-exposed infants when compared with a group of infants not exposed to cocaine or methadone. In addition, their data suggested a higher rate of fetal loss and infant mortality after cocaine exposure in pregnancy. It was noted that episodes of abstinence symptoms occurred less frequently in infants exposed to a combination of cocaine and methadone in 19 of the 21 symptom categories on the Finnegan scale. This trend was not

found to be statistically significant, and thus the conclusion of the authors was that maternal cocaine use had no effect on the severity of neonatal abstinence syptomatology. However, it might be suggested, that had a larger population of infants been studied, there may have been significance to the trend toward a less severe withdrawal course in the cocaine-exposed infants.

That we did not find a significant effect of cocaine on neonatal narcotic withdrawal is most consistent with the results of Ryan et al,[108] Mayes and Carroll,[107] and studies of opiate withdrawal in adults who are also using cocaine.[104] However, Fulroth and colleagues[106] found an increased severity of withdrawal in infants exposed to cocaine in addition to heroin. Three aspects of the present study may account for these differences. The present study prospectively followed women through pregnancy to identify specific drug exposure in the newborn, as opposed to relying solely on the results of urine toxicology at the time of delivery. Second, all infants were followed prospectively for withdrawal symptoms in a study protocol that was pre-defined and monitored specifically for the reduction of bias in scoring. Third, all of the women identified as study subjects were enrolled in a methadone maintenance program, with monitoring for concomitant health problems and illicit drug use.

Methadone dose effect on withdrawal severity

Consistent with previous research,[30, 45, 111] in our study there was a significant positive correlation between maternal methadone dose at the time of delivery and the

severity of withdrawal as measured by the number of days that infants spent on the highest doses of paregoric, and the length of stay of the infant in the hospital. Studies of the predictive factors for the severity of neonatal withdrawal from methadone have most often found maternal methadone dose to be the most significant predictor of withdrawal severity.[30, 45, 111] Doberczak et al[46] found that higher initial plasma methadone levels were associated with more rapid declines of drug levels in methadone-exposed neonates. The more rapid rate of decrease in serum methadone levels after birth correlated significantly with acuity of central nervous system withdrawal signs observed in their sample of infants. In an earlier study by Ostrea et al,[30] neonatal narcotic withdrawal was examined prospectively to determine the effect of multiple factors on severity of symptoms. In a large cohort of infants, they found that the only significant correlation with severity of withdrawal was with the maternal methadone dose. Similarly, in a chart review of 40 women treated with methadone during pregnancy, Malpas et al[112] found a strong association of higher maternal methadone doses with increased length of stay and duration of medication treatment for infants experiencing opiate withdrawal symptoms.

With such clear evidence that maternal methadone dose positively correlates with an increased severity of neonatal withdrawal, it has been suggested that women should be placed on lower-dose methadone regimens in the later stages of pregnancy,[30, 45, 111, 112] or that opiate addicts should be detoxified during pregnancy.[50] In contrast, in our study population, the methadone treatment program tended to increase the daily dose of

methadone when there was evidence that a woman was also using cocaine in pregnancy. Thus, cocaine use could have been indirectly associated with a more severe narcotic withdrawal course. However, it is important to note, there was no difference in the mean methadone dose at the time of delivery between cocaine and non-cocaine users in our study.

In the present study, there was a difference in the total number of weeks that women received methadone during pregnancy. Although not found to be statistically significant, there was a trend toward later enrollment in the methadone program by about four weeks for the mothers who also used cocaine during pregnancy. Thus, women who used cocaine were more likely to have also used illicit opiates for a longer duration during their pregnancy, and may have had lower cumulative exposure to methadone over the gestation. Many have suggested that the relationship between methadone dose and severity of withdrawal is actually due to an accumulation of methadone in fetal tissues which occurs particularly in the last trimester of pregnancy.[27, 109] Also, there is evidence that heroin use during pregnancy produces less severe neonatal withdrawal manifestations than methadone maintenance.[113-116] Therefore, the tendency for infants to be exposed to less cumulative methadone and more heroin *in utero* may account for the trend toward a less severe withdrawal course in our cohort of cocaine-exposed infants.

Benzodiazepine exposure effect

A significant finding from our data was that benzodiazepine (BZD) exposure was associated with longer hospital stays, longer duration of withdrawal medication treatment, and more days at higher doses of paregoric for the infants. The finding of a more severe withdrawal course in these infants was in agreement with published literature on newborn outcome after prenatal BZD exposure. BZDs easily cross the placenta and accumulate in the fetal adipose tissue.[117, 118] There is evidence that neonates have a limited capacity to metabolize BZDs and may experience symptoms of intoxication or passive addiction after prenatal exposure.[119] BZD intoxication symptoms have been described as low Apgar scores, hypotonia, hypothermia, respiratory and neurologic depression.[120] Withdrawal symptoms in newborns exposed to diazepam *in utero* have been described as a high pitched cry, increased muscle tone, and increased regurgitation.[121] Laegreid et al[122] studied 17 infants of women who had been prescribed benzodiazepines during pregnancy, looking at neurologic and behavioral conditions in the neonatal period. Their results were significant for diminished reflexes such as the Moro and optical blink reflexes in infants exposed to BZD, when compared to a reference group of infants without a history of drug exposure. In addition, there were increased findings of drowsiness, tremor, startling, and poor sucking in the BZD-exposed group.

The similarity in clinical appearance of benzodiazepine-exposed and narcotic-exposed infants reveals the difficulty of sorting out the impact of poly-drug exposure on

neonatal outcome. First, testing for benzodiazepines was not routine in the first year of enrollment in our study, and maternal reporting of illicit drug use is not consistently reliable.[5] Thus, infants who were exposed to benzodiazepines may have been missed, and a misclassification of subjects may have occurred. Second, women who were found to be abusing benzodiazepines while on methadone maintenance routinely had the daily doses of methadone increased. In this manner, the effect of benzodiazepines on the severity of narcotic withdrawal symptoms was intensified. Third, the abuse of benzodiazepines may often be associated with an increased severity of illicit opiate abuse or with other drug use in pregnancy. Therefore, the question of the specific effects attributable directly to benzodiazepines is difficult to isolate. In our study, benzodiazepine exposure seemed to correlate with a more severe withdrawal course. However, because there was an even distribution of BZD exposure between the cocaine-exposed and non-cocaine-exposed groups (21.4% and 22.2% respectively) there presumably was equal effect of BZD exposure on the withdrawal symptom scoring in each group in our study.

Pregnancy complications

Although the overall group of poly-drug exposed pregnancies in our study does appear to be at higher risk for complications than non-drug exposed pregnancies, cocaine exposure as a single factor was not associated with an increased risk of poor perinatal outcome in our sample. Our findings are in contrast to the results of others who have

studied cocaine use in pregnancy.[108, 123-125] Most often, cocaine use in pregnancy has been reported to be associated with prematurity, low birth weight, and decreased head circumference.[124, 125] Chasnoff et al[123] studied 52 cocaine-using women and compared them to 73 women who were maintained on methadone during pregnancy. The women in the two separate groups were similar in type of prenatal care, socioeconomic status, and cigarette, marijuana, and alcohol use. The cocaine-using women in the study had significantly higher rates of premature labor, abruptio placentae, fetal monitor abnormality, and fetal meconium staining than women in the methadone group. However, there was no effect of cocaine use on neonatal gestational age, birth weight, length, and head circumference compared to methadone use.

The Chasnoff et al[123] study group was most similar to our own, in that pregnancies complicated by cocaine use were directly compared to those with in which the mothers used methadone. Our cocaine-exposed sample similarly revealed a trend toward a higher rate of preterm labor, and increased fetal distress. Notable due to the reported lessened severity of withdrawal in preterm infants,[109] there was no increased risk of prematurity in the cocaine-exposed group in this study. In addition, we did not find a significant difference between groups in gestational age, birth weight, or head circumference. This apparently low incidence of perinatal morbidity attributable to cocaine exposure is consistent with the results of a meta-analysis evaluation published by Lutiger et al.[126] In their review of 20 papers dealing with the effects of cocaine use during pregnancy on pregnancy outcome, the

analysis revealed very few adverse effects to be significantly associated with cocaine use when compared to control groups of polydrug users. Thus, our results contribute to the suggestion that a variety of adverse reproductive effects commonly quoted to be associated with maternal use of cocaine may be caused by confounding factors clustering in cocaine users.

Study limitations

Failure to find a significant effect of cocaine on neonatal withdrawal may reflect several limitations of the present sample. First, the assignment of infants to cocaine and non-cocaine exposed groups was based on obtaining positive urine screens for cocaine during pregnancy in women enrolled in the methadone maintenance program. Although urine screens were performed routinely and randomly, mothers presenting for methadone treatment later in their pregnancy would be less likely to have had repeated urine screens. Therefore, subjects may have been misclassified as non-cocaine using.

Another problem with the present study was the small number of subjects, and thus the inability to show significant differences between groups due to high standard deviations. Recruitment into the study could have been broadened to include mothers treated at methadone maintenance clinics or delivering at hospitals separate from the YNHH system. However, logistical matters precluded the ease with which drug use information may be shared between institutions. The enrollment of subjects is actively being continued, such

that the sample size of mother and infant pairs may increase, and data may be reanalyzed at another endpoint in the near future.

Thirdly, information on alcohol use during pregnancy was limited for our sample of mothers. Maternal reporting of substance abuse in pregnancy is consistently unreliable and may underidentify users.[5] In addition, there was no objective measure, such as blood alcohol levels, used to detect alcohol consumption in methadone-maintained pregnant women. This becomes important in interpreting results for any study of poly-drug exposed infants. In particular, alcohol exposure during pregnancy has been reported to effect newborn autonomic regulation as evidenced by increased tremors and startles,[127] and by decreased habituation response to novel stimuli such as light or sound.[128] In more recent studies, specific effects on newborn behavior attributable to alcohol exposure have not been detected.[84, 129] However the interactions of cocaine, alcohol, and opiates in newborns are not well understood. This makes it difficult to conclude the amount of effect attributable to cocaine exclusively in our study when there is little information on concomitant alcohol exposure.

A final methodologic issue was the potential for bias to be introduced, particularly in withdrawal scoring and the length of treatment of infants in the hospital. We used the abstinence scoring system devised by Finnegan[33] to quantitate the presence and degree of withdrawal. All scorers were trained in using the scale and were known to be able to score infants accurately. However, the items scored on the Finnegan scale allow for some

subjective input by the scorer, such as the degree of tremors being judged as mild to severe. Such subjectivity in scoring may easily be influenced by observer bias. For instance, the nursing staff at YNHH may have had an idea of whether or not each infant was exposed to other drugs *in utero* in addition to methadone. This information is often gained through other channels than the infant's chart or actual urine assay results, and so may or may not be accurate. To investigate this potential bias, we gathered information on whether scorers believed certain infants were exposed to cocaine prenatally, then compared that opinion with actual urine results from the pregnancies. A brief questionnaire was given to each nurse who had cared for a given infant during hospitalization, asking whether they knew of cocaine exposure in the infant. Data from the nursing staff who cared for 11 of the study infants were gathered and analyzed for accuracy of the predictions. In the overall sample, respondents were unsure of the exposure history 32.9% of the time. However, when nursing staff expressed an opinion that an infant was exposed to cocaine, they were correct 78.0% of the time. Therefore, although blinded to the results of maternal urine analyses, withdrawal scorers often had an idea of whether the infants had been exposed to cocaine *in utero*, and surely held beliefs about how such exposure affected neonatal behavior. Similarly, perceived knowledge of maternal drug use often influences when an infant will be discharged from the hospital, and potentially the length of treatment for withdrawal. Thus, length of stay and duration of treatment as endpoints to a study may be inherently laden with bias.

In conclusion, exposure to cocaine in addition to opiates during pregnancy may not have an effect on the severity of the neonatal abstinence syndrome, as measured by length of treatment, dosage of withdrawal medications, length of stay, and first withdrawal scores. Further investigations that attempt to time more accurately the infant's last exposure to cocaine, as well as to define more clearly the level of alcohol and benzodiazepine exposure will be useful in more precisely defining whether or not cocaine exposure further complicates the withdrawal of the opiate exposed infant. A commonly expressed view among women in methadone maintenance programs is that cocaine use will minimize their infants' withdrawal from methadone. That belief is not supported by the present study, and based on the literature on cocaine exposure in pregnancy many mothers may be placing their infants at increased risk of perinatal morbidity or mortality by adhering to this belief. Thus, there is a strong clinical need for further education and monitoring in the methadone-maintained population of women to detect and decrease polydrug use in pregnancy.

Figure 1

Signs and Symptoms Associated with Neonatal Abstinence

Central Nervous System:

Irritability

High-pitched cry

Exaggerated Moro Reflex

Tremors

Increased Muscle Tone

Increased Deep Tendon Reflexes

Increased Rooting Reflex

Seizures

Metabolic:

Fever

Sweating

Mottling

Gastrointestinal:

Poor Feeding

Regurgitation

Loose Stools

Excessive Sucking

Uncoordinated Sucking

Respiratory:

Respiratory Distress

Frequent Yawning

Nasal Stuffiness

Sneezing

Figure 2

Modified Finnegan Abstinence Scoring Form

		Gms. ____ DATE ____ D	E	N	Gms. ____ DATE ____ D	E	N	Gms. ____ DATE ____ D	E	N
CENTRAL NERVOUS SYSTEM DISTURBANCES:										
Irritability:										
which interferes with ability to sleep at least 2 hours after feeding	1									
which interferes with ability to bottle feed (requiring gavage)	2									
Inconsolable while being held	3									
Mild tremors undisturbed	3									
Moderate-severe tremors undisturbed	4									
Mild tremors disturbed	1									
Moderate-severe tremors disturbed	2									
Increased muscle tone	2									
Excoriation (where _____)	1									
METABOLIC/VASOMOTOR/RESPIRATORY DISTURBANCES:										
Sweating	2									
Fever < 101 (37.2-38.2)	1									
Fever > 101 (≥38.4)	2									
Frequent yawning	1									
Mottling	1									
Nasal stuffiness	1									
Sneezing	1									
Nasal flaring	1									
Respiratory Rate:										
> 60/min	1									
> 60/min with retractions	2									
GASTROINTESTINAL DISTURBANCES:										
Excessive sucking	1									
Poor feeding	2									
Regurgitation	2									
Projectile vomiting	3									
Loose stools	2									
Watery stools	3									

Table 1

Demographic Characteristics of Study Sample

n = 23

	Mean	S.D.	Range
Maternal Age	26.9	5.4	17-38
Number of Pregnancies	3.7	2.0	1-8
Methadone Dose (mg/day)	77.8	22.5	35-120
Weeks on Methadone at Delivery	26.7	12.4	2.5-41

	N (%)
Maternal Ethnicity	
African-American	4 (17.4)
Caucasian	13 (56.5)
Hispanic	6 (26.1)
Maternal HIV Status	
Positive	1 (4.3)
Negative	16 (69.6)
Unknown	6 (26.1)
Maternal Hepatitis Status	
Positive (B or C)	3 (13)
Negative	17 (73.9)
Unknown	3 (13)

Table 2

Infant Study Subjects: Perinatal Data

	Cocaine Negative N=9	Cocaine Positive N=14	
	Mean (S.D.)	Mean (S.D.)	
Gestational Age (wk)	37.9 (3.1)	37.3 (4.2)	F (1,21) = .03
Birthweight (gm)	2677 (620)	2627 (757)	F (1,21) = .12
Head Circumference (cm)	32.2 (2.6)	31.9 (2.7)	F (1,20) = .05
Weight at Discharge (gm)	3396 (1029)	3409 (897)	F (1,21) = .001
Complications:	N (%)	N (%)	
Delivery @ <37 weeks	3 (33.3)	5 (35.7)	
Fetal distress @ delivery	0	2 (14.3)	
Meconium stained fluid	1 (11.1)	0	
Less than 2500 gms	4 (44.4)	5 (35.7)	
Small for Gestational Age	3 (33.3)	1 (7.1)	
Hyperbilirubinemia	3 (33.3)	2 (14.3)	
Infections	0	3 (21.4)	
HIV positive	1 (11.1)	0	
Apnea	1 (11.1)	2 (14.3)	
Other	6 (26.1)	8 (24.2)	
Total number complications	22	28	F (1,21) = .56

Table 3

Infant Withdrawal Course by Cocaine Exposure Status

	Cocaine Negative N=9	Cocaine Positive N=14	
	Mean (S.D.)	Mean (S.D.)	
Length of Stay (d)	36.6 (25.2)	32.9 (14.1)	F (1,21) = .21
Duration of Therapy (d)	30.4 (26.9)	25.8 (14.1)	F (1,21) = .30
First Withdrawal Score	10.3 (6.7)	10.5 (4.6)	F (1,21) = .005
Age at First Withdrawal (hr)	12.7 (10.0)	13.6 (11.7)	F (1,21) = .03
Age at First Medication (hr)	28.2 (23.6)	53.0 (68.8)	F (1,21) = 1.07
Highest Dose Paregoric (drops/24hr)	74.9 (37.5)	82.0 (33.6)	F (1,21) = .22
# Days at Highest Dose	7.9 (11.8)	3.9 (2.1)	F (1,21) = 1.54
Phenobarbital Added (%)	11.1%	14.3%	χ^2 = .05

Table 4

Infant Withdrawal Course by Benzodiazepine Exposure Status

	Benzodiazepine Negative N=18	Benzodiazepine Positive N= 5	
	Mean (S.D.)	Mean (S.D.)	
Methadone Dose at delivery (mg)	71.4 (19.5)	101.0 (14.3)	F (1,21) = 9.92**
Length of Stay (d)	29.2 (13.5)	52.8 (24.7)	F (1,21) = 8.29**
Duration of Therapy (d)	21.8 (13.7)	48.6 (25.0)	F (1,21) = 10.37**
First Withdrawal Score	9.8 (5.6)	12.8 (4.1)	F (1,21) = 1.25
Age at First Withdrawal Score (hr)	15.0 (11.4)	7.0 (5.5)	F (1,21) = 2.24
Age at First Medication (hr)	46.6 (62.2)	31.4 (26.0)	F (1,21) = .28
Highest Dose Paregoric (drops/24hr)	73.6 (35.1)	99.6 (25.3)	F (1,21) = 2.36
# Days at Highest Paregoric Dose	3.7 (3.2)	11.8 (14.4)	F (1,21) = 5.36*
Phenobarbital Added, N(%)	1 (5.6%)	2 (40%)	χ^2 = 4.09*

* $p < .05$

** $p < .01$

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