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COCAINE USE IN PREGNANCY

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Abstract With the increasing use of cocaine in the United States, there has been growing concern regarding its effects on the fetuses and neonates of pregnant cocaine abusers. Twenty-three cocaine-using women enrolled in a comprehensive perinatal-addiction program were divided into two groups: those using cocaine only and those using cocaine plus narcotics. These two groups were compared with a group of women who had used narcotics in the past and were maintained on methadone during pregnancy, and with a group of drug-free women. All four groups were similar in maternal age, socioeconomic status, number of pregnancies, and cigarette, marijuana, and alcohol use. Their medical histories indicated that the cocaine-using women had a significantly higher rate of spontaneous abortion than the women in the other two groups. In the pregnancies under study, four cocaine-using women had onset of labor with abruptio placentae immediately after intravenous self-injection of cocaine. Neonatal gestational age, birth weight, length, and head circumference were not affected by cocaine use. However, the Brazelton Neonatal Behavioral Assessment Scale revealed that infants exposed to cocaine had significant depression of interactive behavior and a poor organizational response to environmental stimuli (state organization).

These preliminary observations suggest that cocaine influences the outcome of pregnancy as well as the neurologic behavior of the newborn, but a full assessment will require a larger number of pregnancies and longer follow-up. (N Engl J Med 1985; 313:666-9.)

WITH the increasing use of cocaine in the United States, there has been a growing interest in the potential medical complications of cocaine use, including its effects on pregnancy, the fetus, and the neonate. In conjunction with the increased use of cocaine in the general population, the number of cocaine-using pregnant women presenting to the Perinatal Addiction Project of Northwestern Memorial Hospital has escalated dramatically, providing an opportunity to evaluate the effects of cocaine on pregnancy and the newborn.

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METHODS

From January 1983 to September 1984, 23 infants were born to cocaine-using women enrolled in the Perinatal Addiction Project of Northwestern Memorial Hospital's Institute of Psychiatry and Prentice Women's Hospital and Maternity Center. During this period, every woman referred to the program for cocaine use during pregnancy was enrolled by the second trimester of pregnancy and was involved in an intensive program that included prenatal care and treatment for chemical dependence. Four women who were referred to the program but refused to be enrolled for treatment were lost to follow-up. None of the women who accepted treatment dropped out of the study. Twice-weekly maternal urine samples were obtained on a regular basis to screen for the use of illicit drugs (opiates, amphetamines, barbiturates, benzodiazepines, propoxyphene, cocaine, or phencyclidine). Alcohol breath tests were performed at the discretion of the patient's counselor to check for alcohol use. In order to evaluate the specific effects of cocaine on pregnancy and the newborn, the cocaine-using women were divided into two groups on the basis of concurrent use or nonuse of narcotics and were compared with two control groups. One control group was

selected from the population of the Perinatal Addiction Project, representing patients maintained on methadone who did not abuse cocaine, and the other control group was selected from among non-addicted pregnant women presenting for prenatal care at the Prentice ambulatory care clinic. Both control groups were matched for maternal age, number of pregnancies, and cigarette and alcohol use.

The 12 women in Group 1 had conceived while using cocaine. These women had no history or evidence of opiate use, but four used alcohol at least twice monthly, and six used marijuana at least three times monthly throughout the first two trimesters of pregnancy. Seven women smoked cigarettes throughout pregnancy. The 11 women in Group 2 had conceived while using both cocaine and heroin. Two of these women used alcohol at least twice monthly, and five used marijuana at least three times monthly throughout the first two trimesters of pregnancy. Eight women smoked cigarettes throughout pregnancy. Upon admission to the project, each woman in Group 2 was given an initial dosage of methadone that corresponded to the amount of opioids she had been using illicitly before admission. This dosage was adjusted to the lowest level that would prevent craving or withdrawal, and by the beginning of the third trimester, each woman was receiving a maintenance dosage of methadone that ranged from 5 to 45 mg per day (mean, 21.8 mg). The methadone dosage was held at the same level for the duration of the pregnancy. Approximately 60 per cent of the women in each of Groups 1 and 2 continued to use cocaine throughout pregnancy. The frequency of cocaine use for the women in Groups 1 and 2 ranged from two to five times per week, and the amount per use ranged from 0.5 to 5 g. All 23 women used cocaine intranasally. In addition, three women in Group 1 and four women in Group 2 also used cocaine intravenously.

The 15 women in Group 3 were opiate abusers selected from the pool of women enrolled in the Perinatal Addiction Project; selection was based on the previously mentioned criteria (age, number of pregnancies, and cigarette, marijuana, and alcohol use). Group 3 women had conceived while using heroin and were converted to methadone maintenance in the same manner as described for Group 2 women. The mean dose of methadone for these women was 17.3 mg per day, with a range of 5 to 40. Three of these women used alcohol at least twice monthly, and seven used marijuana at least three times monthly during the first two trimesters of pregnancy. Eleven women smoked cigarettes throughout pregnancy.

Group 4 comprised 15 women who were not drug abusers, selected from among the patients in a general prenatal care clinic. Despite their lack of involvement in the Perinatal Addiction Project, four of the women had evidence of alcohol use, and two used marijuana in the first two trimesters of pregnancy. Ten of these women smoked cigarettes throughout pregnancy.

The reproductive histories of all the women were reviewed. The addicted women in Groups 1 and 2 had used cocaine, and the Group 3 women had used opiates during all their previous pregnancies. Analysis of variance and chi-square analysis were used for statistical analysis of the maternal indexes that would affect neonatal outcome.

All the neonates were examined at birth, and weight, crown-to-heel length, and fronto-occipital head circumference were recorded. When the infants were three days old, the Brazelton Neonatal Behavioral Assessment Scale[1] was administered by trained examiners who were blinded to the infants' prenatal history. Neonatal data were analyzed by means of a four-way analysis of variance. For the items that reached statistical significance ($P<0.05$), the Multiple Range Test was used to identify differences between subsets.

Results

There were no statistical differences between the four groups in mean maternal age (25.4, 28.7, 25.4, and 26.1 years, respectively). Groups 1 (5 white, 5 black, 2 Hispanic), 2 (5 white, 6 black), 3 (11 white, 3 black, 1 Hispanic) and 4 (4 white, 10 black, 1 Hispanic) were similar in ethnic background (according to chi-square analysis). The incidence and distribution of alcohol, marijuana, and cigarette use in the four groups were statistically similar (chi-square analysis), and there was no significant difference between Groups 2 and 3 in mean daily methadone dosage in the third trimester.

The four groups of women were similar in number of pregnancies, with means of 2.6, 2.8, 3.0, and 2.5 pregnancies, respectively. However, there had been a significantly increased rate of spontaneous abortion in previous pregnancies among the cocaine-using women (analysis of variance, $F = 4.98$, $P<0.005$). Group 1 women had a spontaneous-abortion rate of 38 per cent (mean [±S.D.] number of spontaneous abortions, 0.98 ± 1.1); the Group 2 women's rate was 46 per cent (mean number of spontaneous abortions, 1.3 ± 1.2); and the Group 3 women's rate was 16 per cent (mean number of spontaneous abortions, 0.47 ± 0.9). Since these data were based on patient recall, it was possible to ascertain that the women had been using drugs during previous pregnancies but difficult to determine the temporal relations between specific episodes of drug use and the spontaneous abortions. There was no history of spontaneous abortions in Group 4 women. In the series of pregnancies under study, two women in Group 1 and two women in Group 2 had onset of labor with abruptio placentae in the third trimester immediately after a single intravenous self-injection of cocaine; there were no instances of abruptio placentae in Groups 3 or 4 (chi-square = 5.64; $P<0.05$), two-tailed test.

All the infants were delivered at term as determined by the criteria of Ballard et al.[2] All were singletons, and there was an even distribution of infants according to sex in each group. Apgar scores in the four groups were similar. One infant with prune-belly syndrome, including major malformations of the genitourinary tract, bilateral hydronephrosis, and bilateral cryptorchidism, was born of a woman in Group 1 who had used 4 to 5 g of cocaine in a single day at five weeks' gestation and had had no other cocaine use until the third trimester. There were no other congenital malformations in any infants in any of the groups.

Although infants delivered to methadone-maintained women in Groups 2 and 3 tended to be smaller, there were no statistically significant differences in birth weights, lengths, or head circumferences among infants in the four groups (Table 1).

On the Brazelton scale, infants in Groups 1 and 2, who had been exposed to cocaine, had a greater degree of tremulousness (chi-square = 45, $P<0.002$) and startle responses (chi-square = 31, $P<0.03$) than Group 4 infants, whereas infants in Group 3, who had been exposed to methadone, did not differ from Group 4 infants in these respects. Means and standard deviations for other items on the scale for which significant differences were obtained (analysis of variance) are shown in Table 2. The 47 scores for each infant were divided into four clusters by the a priori cluster method of Als,[3] and analysis of variance was used to compare mean differences in each cluster for the four groups of infants (Table 3). Significant differences were found in the interactive ($F = 3.6$, $P<0.02$) and

Table 1. Measurements of 23 Newborns According to Group.*

	Group 1, Cocaine	Group 2, Cocaine/ Methadone	Group 3, Methadone	Group 4, Control
Weight (g)	3168±508	3127±363	2977±715	3372±624
Length (cm)	49.8±1.9	49.4±2.2	48.6±3.1	50.8±2.9
Head circumference (cm)	33.4±1.9	33.3±1.3	32.9±2.2	34.5±1.7

*Values are means ±S.D.

state organization ($F = 4.4$, $P<0.01$) clusters. Multiple internal comparisons revealed that infants exposed to methadone had significantly worse scores in the interactive cluster than did control infants ($P<0.05$). Infants of cocaine-dependent mothers had significantly worse scores in the state organization cluster than either infants exposed to methadone or control infants ($P<0.05$).

By the age of one month, two cocaine-exposed infants in Group 1 had died; the first died at two weeks of age with a diagnosis of sudden infant death syndrome, and the second died with meningitis, which had its onset at the age of approximately one week. There were no deaths during the neonatal period in any of the other groups.

Discussion

With an estimated 10 million Americans having used cocaine at least once and 5 million using it on a regular basis,[4] it can be assumed that a large number of women have used cocaine while pregnant. There are conflicting reports of cocaine's teratogenicity in animals,[5,6] and the effects of the drug on pregnancy in human beings are also uncertain.

The cocaine-using women in the present study had a higher rate of spontaneous abortion than women who had used heroin during previous pregnancies. Cocaine acts peripherally to inhibit nerve conduction and prevent norepinephrine uptake at the nerve terminals, producing increased norepinephrine levels with subsequent vasoconstriction and tachycardia and a concomitant abrupt rise in blood pressure.[7] Placental vasoconstriction also occurs,[8] decreasing blood flow to the fetus, and with increased norepinephrine levels, an increase in uterine contractility has been reported in human beings.[9] The increased rate of spontaneous abortion found in cocaine-using women in Groups 1 and 2 is consistent with these pharmacologic actions of cocaine.

In the third trimester of pregnancy, several women in Groups 1 and 2 reported feeling contractions and increased fetal activity within minutes of using cocaine. Four women in these two groups experienced the onset of labor with abruptio placentae immediately after self-injection of cocaine. The hypertension and vasoconstriction associated with cocaine use could be responsible for the abruptio placentae, given the association between hypertension and abruptio placentae.[10,11]

The occurrence of prune-belly syndrome in an infant whose mother used a heavy dose of cocaine at five weeks' gestation is consistent with the report of Mahalik et al.,[5] who found an increased incidence of cryptorchidism and hydronephrosis when cocaine was administered to gravid mice on any of Days 7 to 11 of gestation. At five weeks' gestation, the urogenital system is forming in human beings,[12] and a heavy dose of a teratogenic agent as reported by this woman could interrupt mesodermal development and produce the abnormalities noted.[13]

No interference with intrauterine growth was noted in either of the groups of infants exposed to cocaine. This is consistent with reported growth patterns of other infants not exposed to opiates.[14,15] Previous studies by us have revealed significant differences in intrauterine growth for neonates exposed to opi-

Table 2. Mean (±S.D.) Scores on Brazelton Scale Items That Discriminated between Groups.*

	Group 1, Cocaine	Group 2, Cocaine/ Methadone	Group 3, Methadone	Group 4, Control
No. of patients	12	11	15	15
Ankle clonus	1.0±0.5†	0.99±0.9	1.2±1.1	1.9±0.5
Standing	1.4±0.5†	1.3±0.5	1.7±0.9	2.0±0.1
Automatic walking	1.2±0.4†	1.0±0.4	1.4±0.7	1.8±0.4
Moro reaction	2.2±0.7†	1.7±0.4	1.4±0.8	1.8±0.4
Inanimate visual orientation	3.0±2.7†	4.0±2.7	3.1±2.0	5.7±2.1
Inanimate auditory orientation	2.3±1.1†	4.6±2.0	3.5±1.4	5.5±2.5
Animate visual orientation	3.2±2.5†	5.4±2.0	3.4±1.6	5.9±2.1
Animate auditory orientation	2.8±1.7†	5.9±1.9	3.5±1.7	5.9±2.5
Animate visual and auditory orientation	3.7±3.0†	6.1±2.2	4.2±2.3	6.5±1.9
Motor maturity	4.2±1.4†	4.1±2.2	3.0±1.4	5.0±1.7
Pull to sit	5.5±2.0†	5.1±2.6	4.0±1.8	6.2±1.4
Consolability	2.3±1.7‡	4.6±1.6	4.6±2.6	6.3±1.3
Lability of skin color	6.5±2.0†	4.7±1.9	5.1±2.4	3.1±1.7
Lability of states	4.6±1.3†	4.0±1.3	4.2±2.6	2.6±1.0

*Items on the Brazelton Neonatal Behavioral Assessment Scale for which significant differences were found by analysis of variance.

†Value is significantly different from that in Group 4 (Multiple Range Test) by analysis of variance ($P<0.02$).

‡Value is significantly different from those in Groups 2, 3, and 4 (Multiple Range Test) ($P<0.0006$).

Table 3. Mean (±S.D.) Scores for Clusters of Items on the Brazelton Scale, According to Group.*

	Group 1, Cocaine	Group 2, Cocaine/ Methadone	Group 3, Methadone	Group 4, Control
Interactive	2.8±0.4	2.5±0.7	2.9±0.4†	2.1±0.9
Motoric	2.3±0.5	2.4±0.7	2.1±0.3	1.9±0.4
State organization	2.4±0.5‡	2.1±0.4	1.9±0.3	2.0±0.2
Physiologic§	1.0±0	1.0±0	1.0±0	1.0±0

*Analysis of variance was used to compare the mean differences in each cluster for the four groups of infants.
†Value is significantly different from that in Group 4 (Multiple Range Test, $P<0.02$).
‡Value is significantly different from those in Groups 3 and 4 (Multiple Range Test, $P<0.01$).
§All the physiologic-cluster scores fell within the normal range, and there was no variation.

ates. The absence of such differences in the methadone-exposed infants most likely represents a Type II error due to the relatively small number of infants. The occurrence of sudden death in one infant from Group 1 raises the issue of an increased risk of sudden infant death syndrome in infants exposed to cocaine in utero. Although an increased risk of the syndrome has been reported for infants born to women addicted to narcotics,[16] larger numbers of infants exposed to cocaine will need to be followed before the risk of sudden infant death in this group can be ascertained.

Previous reports of differences in neurobehavior detected by the Brazelton scale between drug-free infants and infants delivered to methadone-maintained women,[14] women who used phencyclidine during pregnancy,[15] and women addicted to pentazocine and tripelennamine during pregnancy[17] have shown consistent patterns of depressed interactive behavior and state control among the drug-exposed neonates. This was confirmed in the present study by the findings of depressed interactive abilities and significant impairment in organizational abilities in infants exposed to cocaine as compared with control infants or with infants whose mothers used methadone. It is evident from these findings that cocaine exposure in utero interferes with an infant's ability to maintain adequate state control in the neonatal period — a factor that places infants exposed to cocaine in a category of high risk similar to that of infants exposed to narcotics in utero.

Although the Group 2 infants (cocaine/methadone) showed weaker reflexes and poorer state control than the control infants in Group 4, they had no significant deficits in auditory or visual orientation. This lack of significant deficiencies in orientation responses among the Group 2 neonates could represent a Type II error. The use of alcohol, marijuana, and nicotine was similar in all four groups and therefore probably does not account for these findings. It is possible to speculate that in the Group 2 infants, who were exposed in utero to both a central nervous system depressant (methadone) and a central nervous system stimulant (cocaine), there was an interaction in which each of the drugs antagonized the effects of the other. Whether or not these effects occur in the fetus or neonate is currently unknown. In addition, the dosages of the drugs used, frequency of use, contaminants used to adulterate the street drugs abused, and other factors may be important in relation to their effects on fetal and neonatal development.

It is apparent from this study that cocaine exerts an influence on the outcome of pregnancy as well as on neonatal neurobehavior. It is also possible to infer from these data that infants exposed to cocaine are at risk for a higher rate of congenital malformations and perinatal mortality. Continuation of these studies with larger numbers of infants is necessary to verify these findings and to evaluate the possibility of other problems associated with cocaine use during pregnancy. Long-term follow-up of the infants in this study is currently under way to determine whether there are permanent sequelae related to intrauterine exposure to cocaine.

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