Temporal Patterns of Cocaine Use in Pregnancy

Perinatal Outcome

Ira J. Chasnoff, MD; Dan R. Griffith, PhD; Scott MacGregor, DO; Kathryn Dirkes, BME; Kayreen A. Burns, PhD

Seventy-five cocaine-using women enrolled in a comprehensive perinatal care program were divided into two groups: those who used cocaine in only the first trimester of pregnancy (group 1 [N = 23]) and those who used cocaine throughout pregnancy (group 2 [N = 52]). Perinatal outcomes of these pregnancies were compared with perinatal outcomes of a matched group of obstetric patients with no history or evidence of substance abuse (group 3 [N = 40]). Group 2 women had an increased rate of preterm delivery and low-birth-weight infants as well as an increased rate of intrauterine growth retardation. Group 1 women had rates of these complications similar to the drug-free group. Mean birth weight, length, and head circumference for term infants were reduced in only the group 2 infants. However, both groups of cocaine-exposed infants demonstrated significant impairment of orientation, motor, and state regulation behaviors on the Neonatal Behavioral Assessment Scale.

(*JAMA* 1989;261:1741-1744)

THE IMPACT of cocaine on American society has been documented repeatedly in the past few years,[1-3] but its effect on human reproduction has only relatively recently been appreciated.[4-6] Women of childbearing age comprise an increasing proportion of all cocaine users in the United States,[7] but information regarding the effects of cocaine taken during pregnancy on the developing fetus and newborn infant is sparse and thus far has focused only on cocaine users as a group. There is no information regarding the relationship of patterns of cocaine use in pregnancy and differential effects on outcome of pregnancy and the newborn infant. In this report, the cocaine-use patterns of 75 pregnant women are studied and perinatal outcomes compared with the pregnancy outcomes of a matched group of obstetric patients with no history or evidence of substance abuse.

From the Departments of Pediatrics (Dr Chasnoff and Ms Dirkes), Psychiatry and Behavioral Sciences (Drs Chasnoff, Griffith, and Burns), and Obstetrics and Gynecology (Dr MacGregor), Northwestern University Medical School, Chicago.

Reprint requests to 215 E Chicago Ave, Suite 501, Chicago, IL 60611 (Dr Chasnoff).

METHODS

The Perinatal Center for Chemical Dependence at Northwestern University Medical School was established in 1976 to provide a comprehensive program of psychiatric, obstetric, and follow-up pediatric care to substance-abusing pregnant women and their infants. From Jan 1, 1986, to Feb 1, 1988, one hundred thirty-eight women who had used cocaine during their pregnancies received complete prenatal care at the Perinatal Center for Chemical Dependence. Of these women, 109 had no concomitant opiate use. Those women who used opiates with cocaine were eliminated from the study. All women were enrolled by the 12th week of pregnancy and received intensive obstetric care through the remainder of the pregnancy. The average number of prenatal visits was 14 (range, nine to 20). The goal of intervention was to bring the women to abstinence. Urine toxicological analysis through Enzyme-Multiplied Immunoassay Technique screening was performed at admission, with positive results confirmed by gas chromatography/mass spectrometry. At each prenatal obstetric visit, urine specimens for toxicological analysis were obtained and current substance abuse was reviewed. History and toxicology studies covered the following substances: caffeine, nicotine, barbiturates, cocaine and its metabolites, opiates, benzodiazepines, propoxyphene, phencyclidine, amphetamines, alcohol, and marijuana. All obstetric and neonatal data were collected prospectively.

To specifically evaluate the effect of first-trimester cocaine use vs use throughout pregnancy, women who used cocaine in only the second trimester (N = 2), in only the third trimester (N = 5), in the first and second trimester (N = 10), in the first and third trimester (N = 10), and in the second and third trimester (N = 7) were not included in the present study. The remaining cocaine-using women were divided into two groups. The first group (group 1) consisted of 23 women who used cocaine during the first weeks of pregnancy, but who attained abstinence by the end of the first trimester and reported no further cocaine use throughout their pregnancy, as documented by ongoing chemical dependence evaluation and urine toxicological testing. The second group

Downloaded from www.jama.com by guest on January 25, 2010

of cocaine-using women (group 2) consisted of 52 women who conceived while addicted to cocaine and continued to use cocaine throughout their pregnancy.

For comparison, a control group with no history or evidence of drug use confirmed on random urine toxicological testing (group 3 [N = 40]) was selected from the general obstetric population receiving care throughout pregnancy at the same hospital. Group matching was performed on the basis of maternal age, socioeconomic class, and tobacco use. No women in any of the three groups were receiving medication or had additional medical problems.

All neonates were examined at birth by a physician blinded to the infant's prenatal history, and weight, crown-to-heel length, and fronto-occipital head circumference were recorded. Gestational age assessment was performed through use of the evaluation of Ballard et al[8] and each infant's birth weight was plotted for gestational age on fetal growth curves developed by Brenner et al.[9] When the infants were 12 to 72 hours old, the Neonatal Behavioral Assessment Scale (NBAS)[10] was administered by trained examiners who were blinded to the infants' prenatal history. Infants delivered prior to 38 weeks' gestation were not included in the NBAS data analysis.

Pregnancy and neonatal data were analyzed by the use of χ^2 analysis for nonparametric data or by a one-way analysis of variance (ANOVA) for parametric data with cocaine use as the independent variable in the three groups. For items that reached statistical significance ($P<.05$) on ANOVA, the Scheffé Procedure was used to identify differences between subsets.

RESULTS

Groups 1, 2, and 3 were similar (by ANOVA) for mean maternal age (25.4 ± 4.2 [SD], 27.5 ± 4.4, and 26.8 ± 4.8 years, respectively), prenatal weight gain (12.4 ± 4.5, 12.2 ± 5.4, and 12.8 ± 5.3 kg, respectively), and cigarettes smoked per day (9.8 ± 9.4, 10.1 ± 8.1, and 8.0 ± 10.8, respectively). Groups 1 (six whites, 11 blacks, and six Hispanics), 2 (18 whites, 28 blacks, and six Hispanics), and 3 (16 whites, 19 blacks, and five Hispanics) were similar for racial distribution, gravidity, and parity (χ^2 analysis).

Women in each cocaine group used an average of ½ g of cocaine (range, ¼ to 5 g) with each use. Similar numbers of women in each group snorted (40%) or free-based (50%) the cocaine, while the remaining women used cocaine intravenously. None of the obstetric or neonatal outcomes reported herein were significantly affected by the amount, frequency, or route of cocaine use.

Table 1.—Perinatal Complications

Complication	Group 1 (Cocaine*), No. (%) (N = 23)	Group 2 (Cocaine†) No. (%) (N = 52)	Group 3 (Drug Free), No. (%) (N = 40)	P‡
Preterm delivery§	4 (17)	16 (31)	1 (3)	<.003
Low birth weight‖	0 (0)	13 (25)	2 (5)	<.003
Small for gestational age¶	0 (0)	10 (19)	1 (3)	<.01
Abruptio placentae	2 (9)	8 (15)	0 (0)	<.05

*Cocaine used in only the first trimester of pregnancy.
†Cocaine used throughout pregnancy.
‡χ^2 analysis.
§Less than 38 weeks' gestation.
‖Less than 2500 g.
¶Less than tenth percentile by birth weight curve of Brenner et al.[9]

Table 2.—Neonatal Growth Parameters for Full-Term Infants

Parameter	Group 1 (Cocaine*), X̄ (SD) (N = 19)	Group 2 (Cocaine†), X̄ (SD) (N = 36)	Group 3 (Drug Free), X̄ (SD) (N = 39)	P‡
Weight, g	3160 (453)	2829§ (708)	3436 (628)	<.001
Length, cm	49.3 (2.5)	48§ (3.6)	51.1 (2.9)	<.001
Head circumference, cm	33.4 (2.2)	32.7§ (2.3)	34.6 (1.6)	<.001

*Cocaine used in only the first trimester of pregnancy.
†Cocaine used throughout pregnancy.
‡Analysis of variance.
§Significant difference from group 3 (Scheffé Procedure).

Alcohol use was similar in the two drug-using groups. Three women (13%) in group 1 and six women (12%) in group 2 drank more than 60 mL of alcohol per week in the first trimester. Average absolute alcohol used by the three women in group 1 and the six women in group 2 was 39.9 ± 119 and 19.4 ± 41 mL per week, respectively. Incidence of marijuana use was similar for the two drug-using groups, with ten women (43%) in group 1 and 20 (38%) in group 2 using marijuana in the first trimester (mean, 5.0 ± 9.0 and 6.5 ± 15.7 joints per month, respectively). Only one woman in group 1 and two women in group 2 used marijuana or alcohol beyond the first trimester. No woman in group 3 used marijuana or alcohol.

There was no difference in sex distribution or in incidence of low Apgar scores (<7) at one and five minutes between the three groups. Infants born to women who used cocaine throughout pregnancy (group 2) had a significantly ($F[2,112] = 8.9$; $P<.001$) lower mean gestational age (38.0 ± 2.8 weeks) than infants in the drug-free group (39.8 ± 0.7 weeks). However, infants born to women who abstained from cocaine after the first trimester had a mean gestation (38.9 ± 1.5 weeks) that was not significantly different from either the drug-free group or infants whose mothers used cocaine throughout pregnancy.

The rate of premature delivery was increased in group 2 compared with group 3 (Table 1), but there was no significant difference in the rate of premature delivery between groups 1 and 2 or groups 1 and 3. The incidence of low birth weight and small-for-gestational-age infants was increased in the group 2 pregnancies (Table 1) as compared with both group 1 and group 3 infants. Use of cocaine in only the first trimester was associated with a rate of abruptio placentae similar to the abruption rate for women who used cocaine throughout pregnancy (Table 1).

Evaluation of neonatal growth parameters for all term (≥38 weeks' gestation) infants showed that infants born to mothers who used cocaine throughout pregnancy had a lower mean weight, length, and head circumference at birth compared with the drug-free infants. Infants born to mothers who used cocaine during only the first trimester did not demonstrate significant deficiencies in intrauterine growth (Table 2).

Neonatal complications were found in both of the cocaine-exposed groups. Two infants born to women who used cocaine throughout pregnancy had ileal atresia presenting in the first 24 hours after birth. Six infants born to women

Downloaded from www.jama.com by guest on January 25, 2010

Table 3.—NBAS* Cluster Score Comparisons for Full-Term Cocaine-Exposed and Drug-Free Infants

NBAS Clusters	Group 1 (Cocaine†) (N = 16)	Group 2 (Cocaine‡) (N = 36)	Group 3 (Drug-Free) (N = 37)	F Scores
Habituation	4.5	4.7	3.7	$F(2,72) = 1.23$
Orientation	1.6§	2.6§	5.5	$F(2,86) = 27.21$‖
Motor	3.4¶	4.0§	5.1	$F(2,86) = 25.21$‖
State range	3.5	3.6	3.1	$F(2,86) = 3.88$‖
State regulation	2.7§	3.5§	5.1	$F(2,86) = 15.45$‖
Autonomic regulation	6.1	6.2	6.5	$F(2,86) = 0.71$
Abnormal reflexes	3.6§	3.4§	1.6	$F(2,86) = 7.41$‖

*NBAS indicates Neonatal Behavioral Assessment Scale.
†Cocaine used in only the first trimester of pregnancy.
‡Cocaine used throughout pregnancy.
§Significant difference from group 3 (Scheffé Procedure [$P \leq .05$]).
‖Significant F ratio ($P \leq .05$).
¶Significant difference from group 2 and group 3 (Scheffé Procedure [$P \leq .05$]).

who used cocaine throughout pregnancy had seizures during the neonatal period. These six infants were all born with cocaine and active metabolites in the urine at the time of birth. Results of a complete work-up including serum calcium and glucose level measurement, lumbar puncture, and computed tomography of the head were normal for all six infants. Two infants had an abnormal electroencephalogram and the remaining four were normal. Two additional infants in group 2 born to mothers who used cocaine in the two to three days prior to delivery suffered perinatal cerebral infarctions. Genitourinary tract abnormalities occurred in three infants born to mothers who used cocaine only in the first trimester of pregnancy and six infants whose mothers used cocaine throughout their pregnancy. Among these nine infants, two male infants had prune-belly syndrome, one female infant had female pseudohermaphroditism, three infants had hydronephrosis, one infant had unilateral hydronephrosis with renal infarction of the opposite kidney, and two infants had isolated secondary hypospadias.

Infants assessed with the NBAS between 12 and 72 hours of age included 16 whose mothers used cocaine during the first trimester of pregnancy only (group 1), 36 whose mothers used cocaine throughout pregnancy (group 2), and 37 whose mothers were drug free during pregnancy (group 3). These groups were somewhat smaller than other groups that were analyzed for the medical variables because of the elimination of premature infants (gestational age <38 weeks) from the sample and the fact that some infants were delivered on the weekend and were released from the hospital before they could be assessed with the NBAS.

Neonatal Behavioral Assessment Scale results for the infants revealed significant differences between the drug-free infants and the two groups of cocaine-exposed infants on a number of variables (Table 3). Infants' performances on a priori clusters established by Lester et al[11] indicated that both groups exposed to cocaine demonstrated significant impairment as compared with the drug-free group in the areas of orientation, motor ability, and state regulation and number of abnormal reflexes. Group 2 infants received a significantly higher mean score on the state range cluster than group 3 infants. Group 1 performance on the motor cluster was significantly below that of group 2. No significant differences were found between the three groups on the cluster scores representing habituation, state range, or autonomic regulation.

An examination of the individual orientation cluster scores illustrates the severity of the cocaine-exposed infants' orientation difficulties. All of the 37 drug-free controls (group 3) were able to achieve an alert state and engage in varying degrees of responsivity with the examiner. By comparison, seven of the 16 group 1 infants exposed to cocaine during only the first trimester and eight of the 36 group 2 infants exposed to cocaine throughout pregnancy were unable to reach alert states at all and consequently were unable to engage in any orientation. There was a significant difference between group 1 and group 3 ($\chi^2 = 15.03$; $P \leq .0001$) and between group 2 and group 3 ($\chi^2 = 7.10$; $P \leq .01$) in terms of number of infants who were unable to achieve alert states.

COMMENT

Current studies have shown that a significant number of women in the prime childbearing age range of 18 to 35 years are actively using cocaine.[7] Many of these women become pregnant and continue to use cocaine without realizing that they are pregnant. Thus, it is important to evaluate the effects of cocaine use in early pregnancy rather than its effects only when used throughout pregnancy. In addition, development of intervention programs for cocaine-using pregnant women will necessarily rely on information regarding the possibility of improved outcome for pregnancies in which a woman stops using cocaine in the first trimester of pregnancy.

In this study, surprisingly, the rate of abruptio placentae did not decrease if a woman abstained from cocaine in the last two trimesters of pregnancy. It has been hypothesized that the high rate of abruptio placentae in cocaine-exposed pregnancies is related to the acute hypertension produced by cocaine use.[4,12] However, in this study it appears that the damage done to placental and uterine vessels in early pregnancy by the cocaine may place these pregnancies at continued risk even if cocaine use ceases.

Recent studies have found that maternal cocaine use is related to intrauterine growth retardation.[6] In this study, infants exposed to cocaine throughout pregnancy had a significant decrease in mean birth weight, length, and head circumference compared with the control infants. It has been hypothesized[6] that this decrease in intrauterine growth is related to the intermittent diminution of placental blood flow associated with maternal cocaine use.[13] Infants whose mothers used cocaine only in the first trimester had improved intrauterine growth and, in fact, the infant's weight, length, and head circumference were not significantly reduced from that of drug-free control infants.

The interactive effect of alcohol, marijuana, and tobacco use with cocaine to produce growth impairments in those pregnancies with significant secondary drug use cannot be completely evaluated at this point. It can be said only that the infants exposed to cocaine in the first trimester (group 1) were exposed to similar amounts of alcohol, marijuana, and tobacco as the second group of cocaine infants and use of alcohol and marijuana for the majority of women in the two cocaine groups was minimal compared with cocaine use.

Analysis of outcome data within each cocaine group did not show a significant relationship with amount of cocaine ingested with each use or with frequency of use. However, since the women in this study were enrolled in a chemical dependence program, the amount and frequency of use were relatively high, with a narrow range. Larger numbers of subjects, including those with mini-

Downloaded from www.jama.com by guest on January 25, 2010

mal cocaine use, will be necessary to study these relationships more fully.

A recent study[14] completed at the Perinatal Center for Chemical Dependence demonstrated genitourinary tract malformations in infants exposed to cocaine in pregnancy. In this study, nine infants had such malformations. An increased incidence of neural tube defects has been reported by Bingol et al.[5] No infants in either cocaine-exposed group in this study exhibited neural tube defects, although one infant in our program whose mother used cocaine in the first and third trimesters, and thus was not included in the present study, had a myelomeningocele at birth. Two cases of ileal atresia occurred among the cocaine-exposed infants in this study. The ileal atresia that occurred in two infants could be secondary to intrauterine bowel infarction.[15]

The pharmacologic action of cocaine is consistent with the abnormalities found among the cocaine-exposed infants. Cocaine acts at the nerve terminals to prevent dopamine and norepinephrine reuptake, producing increased circulating levels of these catecholamines.[16] Subsequent vascoconstriction and tachycardia occur. Placental vasoconstriction is marked,[18] decreasing blood flow to the fetus. The fetal hypoxia induced by this vasoconstriction could not only explain the intrauterine growth retardation,[17] but the intermittent vascular disruptions could result in the increased rate of malformations[15,18] as well.

Cocaine use in young adults has been shown to lower the seizure threshold, placing young adult cocaine users at increased risk for seizures.[1,3] Six infants among the cocaine-exposed infants had seizures in the neonatal period. All six of these infants had cocaine or metabolites present in urine at the time of delivery, although the seizures did not necessarily occur when cocaine was present.

Two infants whose mothers used cocaine in the two days prior to delivery suffered cerebral infarctions that were thought to have occurred in the perinatal period.[19] The cardiovascular effects of cocaine have been well documented and myocardial and cerebral infarctions have been found in increasing numbers of young adults who use cocaine.[1,2]

The results of this study confirm earlier findings that exposure to cocaine during the prenatal period leads to significant impairment in neonatal neurobehavioral capabilities.[4,20] This study further indicates that the neurobehavioral response deficiencies occur in the cocaine-exposed infant whether the mother stops cocaine use in the first trimester or uses cocaine throughout the pregnancy. Although NBAS scores tended to be lower in group 1 compared with group 2 infants, there was no statistically significant difference between the two groups except for the motor cluster. Larger groups of infants will need to be evaluated before relative performance between the two groups can be fully delineated.

It appears, however, that cocaine exposure in only the first trimester does place the newborn at risk for neurobehavioral deficiencies compared with drug-free infants. In normal human fetal development, norepinephrine, serotonin, and dopamine are among the first neurotransmitters present at early stages of brain development, having been shown to be present in the 3- to 4-month fetus.[21] The protective function of the blood-brain barrier is not well developed in the young fetus[22]; thus, cocaine may act on fetal brain neurotransmitters in the first trimester and induce subtle behavioral changes evident in the newborn infant. Animal studies with monosodium glutamate and diazepam have shown that neonatal rats exposed to monosodium glutamate early (day 7 to day 20) in gestation demonstrated behavioral deficits in complex discrimination similar to newborn rats exposed to diazepam in late gestation.[22]

Cocaine's action in blocking norepinephrine and dopamine reuptake could interfere with some aspects of neuronal development. Grimm[22] has hypothesized that such interference could initiate compensatory neurochemical mechanisms that would partially correct for the abnormalities but still leave the infant impaired in his or her ability to cope with complex environmental demands at some point in later life. The neurodevelopmental deficiencies exhibited by the infants exposed to cocaine in only the first trimester lend credence to this hypothesis.

Conclusions developed from this study have implications for both intervention and prevention. For women who become pregnant and are users of cocaine, intervention in early pregnancy with cessation of cocaine use will result in improved obstetric and neonatal outcome. However, prevention programs aimed at educating adolescents and women of childbearing age as to the dangers of cocaine use in pregnancy must be initiated, since even early fetal cocaine exposure places the child at risk for neurobehavioral outcome and may have implications for long-term development.

This investigation was supported by grant DA04103 from the National Institute on Drug Abuse, Rockville, Md.

References

1. Cregler L, Mark H: Medical complications of cocaine abuse. *N Engl J Med* 1986;315:1495-1500.
2. Isner JM, Estes NAM III, Thompson PD, et al: Acute cardiac events temporarily related to cocaine abuse. *N Engl J Med* 1986;315:1438-1443.
3. Jonsson S, O'Meara M, Young JB: Acute cocaine poisoning: Importance of treating seizures and acidosis. *Am J Med* 1983;75:1061-1064.
4. Chasnoff IJ, Burns WJ, Schnoll SH, et al: Cocaine use in pregnancy. *N Engl J Med* 1985;313:666-669.
5. Bingol N, Fuchs M, Diaz V, et al: Teratogenicity of cocaine in humans. *J Pediatr* 1987;110:93-96.
6. MacGregor SN, Keith LG, Chasnoff IJ, et al: Cocaine use during pregnancy: Adverse perinatal outcome. *Am J Obstet Gynecol* 1987;157:686-690.
7. Clayton RR: Cocaine use in the US: In a blizzard or just being snowed, in Kozel NJ, Adams EH (eds): *Cocaine Use in America: Epidemiology and Clinical Perspectives*, NIDA research monograph 61. Rockville, Md, US Dept of Health and Human Services, 1985, pp 8-34.
8. Ballard JL, Kazmaier K, Driver M: A simplified assessment of gestational age, abstracted. *Pediatr Res* 1977;11:374.
9. Brenner WE, Edelman DA, Hendricks CH: A standard of fetal growth for the United States of America. *Am J Obstet Gynecol* 1976;126:555-564.
10. Brazelton TB: *Neonatal Behavioral Assessment Scale*. Philadelphia, Spastics International, 1968.
11. Lester BM, Als H, Brazelton TB: Regional obstetric anesthesia and newborn behavior: A reanalysis towards synergistic effects. *Child Dev* 1982;253:687-692.
12. Acker D, Sachs BP, Tracey KJ, et al: Abruptio placentae associated with cocaine use. *Am J Obstet Gynecol* 1983;146:220-221.
13. Moore TR, Sorg J, Miller L, et al: Hemodynamic effects of intravenous cocaine on the pregnant ewe and fetus. *Am J Obstet Gynecol* 1986;155:883-888.
14. Chasnoff IJ, Chisum GM, Kaplan WE: Maternal cocaine use and genitourinary tract malformations. *Teratology* 1988;37:201-204.
15. Woods JR, Plessinger MA, Clark KE: Effect of cocaine on uterine blood flow and fetal oxygenation. *JAMA* 1987;257:957-961.
16. Ritchie JM, Greene NM: Local anesthesia, in Gilman AG, Goodman LS, Gilman A (eds): *The Pharmacologic Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co Inc, 1980, pp 300-320.
17. Van Allen MI: Fetal vascular disruption: Mechanisms and some resulting birth defects. *Pediatr Ann* 1981;10:219-233.
18. Stevenson RE, Kelly JC, Aylsworth AS, et al: Vascular basis for neural tube defects: A hypothesis. *Pediatrics* 1987;80:102-106.
19. Chasnoff IJ, Bussey ME, Savich R, et al: Perinatal cerebral infarction and maternal cocaine use. *J Pediatr* 1986;108:456-459.
20. Chasnoff IJ, Burns KA, Burns WJ: Cocaine use in pregnancy: Perinatal morbidity and mortality. *Neurobehav Toxicol Teratol* 1987;9:291-293.
21. Nobin A, Bjorklund A: Topography of the monoamine neuron systems in the human brain as revealed in fetuses. *Acta Physiol Scand Suppl*, 1973, suppl 388, pp 1-40.
22. Grimm VE: Effect of teratogenic exposure on the developing brain: Research strategies and possible mechanisms. *Dev Pharmacol Ther* 1987; 10:328-345.

Downloaded from www.jama.com by guest on January 25, 2010