

Growth of Infants Prenatally Exposed to Cocaine/Crack: Comparison of a Prenatal Care and a No Prenatal Care Sample

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ABSTRACT. *Objective.* It has not been possible to draw firm conclusions about the effects of prenatal cocaine exposure because of methodologic problems involved in the conduct of this research. This study, designed to overcome some of these methodologic problems, is a prospective, longitudinal investigation of the effects of prenatal cocaine/crack exposure on neonatal growth in two samples, one with and one without prenatal care (PC).

Methods. Women in the PC sample ($n = 295$) were interviewed at the end of each trimester about their use of cocaine, crack, alcohol, tobacco, marijuana, and other drugs. Women in the no prenatal care (NPC) sample ($n = 98$) were interviewed at delivery about their drug use during each trimester of pregnancy. In both samples, information was also obtained about sociodemographic, lifestyle, psychologic, and social support characteristics. Both samples consisted of women who were predominantly low income, single, and high school educated. Of the women, 48% in the PC sample were black; 81% in the NPC sample were black. Infants were examined during the postpartum hospital stay by project nurses who were blind to maternal substance use status.

Results. Women in both samples who used cocaine/crack during pregnancy were older, had lower family incomes, and used more alcohol than did women who did not use cocaine/crack during pregnancy. In addition, women in the NPC sample were more likely to be black, less educated, gained less weight during pregnancy, and used more alcohol than did women in the PC sample, regardless of cocaine use. In both samples, cocaine/crack use during early pregnancy predicted reduced gestational age, birth weight, length, and head circumference, after controlling for the significant covariates of cocaine use. In a comparison of the samples, the offspring of the NPC/cocaine group were significantly smaller than were the offspring of the PC/no cocaine group, whereas the offspring of the PC/cocaine and NPC/cocaine groups did not differ.

Conclusions. These results indicate that exposure to cocaine/crack during early pregnancy decreases the intrauterine growth of exposed offspring in women with and without PC. Each of the growth parameters was affected indicating symmetric growth retardation. The adequacy of PC was not a significant factor in determining the difference between cocaine-exposed and nonexposed infants. These samples are being followed throughout

childhood to determine whether there are long-term effects of prenatal cocaine/crack exposure on growth. *Pediatrics* 1999;104(2). URL: <http://www.pediatrics.org/cgi/content/full/104/2/e18>; prenatal cocaine/crack use, neonatal growth, prenatal care.

ABBREVIATIONS. GA, gestational age; PC, prenatal care; NPC, no prenatal care; SGA, small-for-gestational age; LBW, low birth weight.

Research on the effects of prenatal cocaine exposure on neonatal growth has produced conflicting results. Some investigators have reported that prenatal cocaine exposure is associated with decreased birth weight, length, or head circumference.¹⁻¹⁰ Other studies have found no significant effects of prenatal cocaine exposure on neonatal growth.¹¹⁻¹⁹ Some studies have shown an increased rate of prematurity or a lower mean gestational age (GA) in infants exposed to cocaine,^{1,6,8,9,14,16,20,21} whereas other studies have not.^{7,10,17,22-24}

Lutiger et al²⁵ performed a meta-analysis and found that cocaine exposure had a moderate effect size on, birth weight, length, head circumference, and GA compared with no cocaine exposure during gestation. However, there were no significant effects on growth when polydrug/cocaine users were compared with polydrug/no cocaine users. In addition to these inconsistencies among the results of published studies, Koren et al²⁶ demonstrated that there has been a bias toward rejecting studies that report no effects of cocaine, although many such studies have been methodologically superior to studies showing effects. Thus, it is not possible to draw firm conclusions about the effects of prenatal cocaine exposure.

Differences in findings among previous studies are most likely attributable to the host of methodologic problems involved in studying the effects of prenatal cocaine use.^{27,28} Many studies have used samples that are not representative of the general population of pregnant cocaine users, for example, studies that have selected subjects from comprehensive prenatal drug treatment programs, at delivery based on a positive urine screen, or based on a lack of prenatal care (PC).

In addition, accurate measurement of substance use in pregnant women is a difficult task. Maternal willingness to report alcohol and drug use is influenced by fear of punitive measures, issues of confidentiality, interviewer training and sensitivity, and

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the type of questionnaire. Urine toxicology detects only recent cocaine use and therefore tends to yield a sample of women who used more frequently.¹⁰ In more representative samples, pregnant women change their pattern of substance use as pregnancy progresses.^{29,30} Measures such as meconium and hair analysis are used by some researchers. These assessments have the advantage of providing measurement over a longer period, but they do not provide accurate information on the amount, timing, and duration of cocaine use. Data on the pattern of substance use are critical when evaluating the effect of a potential teratogen.

It is also critical to consider the covariates of cocaine use, such as demographic and socioeconomic characteristics and tobacco, alcohol, and other illicit drug use, each of which influences neonatal outcome. The adverse effects attributed to prenatal cocaine use may be caused instead by these confounding variables, an interpretation for which we²⁸ and others^{25,31} have found evidence. In addition, it is difficult to compare the results of even well-designed studies when there are substantial differences in the sociodemographic and substance use characteristics of the samples.^{18,32}

In addition to differences in sociodemographic and substance use characteristics, women who use cocaine generally receive less adequate PC than do women who do not use cocaine prenatally.^{33,34} Adverse effects of poor PC include increased rates of low birth weight (LBW) and mortality.^{35,36} Some samples of women who use substances during pregnancy consist entirely of women who received no prenatal care (NPC); other samples include women who received varying amounts of PC.

Women who use cocaine and receive inadequate PC have poorer outcomes than do women who use cocaine and receive PC.³⁷⁻⁴⁰ Generally, previous studies have compared these two groups with women who did not use cocaine prenatally and received PC but have not had a comparison group of women who did not use cocaine and who did not receive adequate PC. A recent study by Berenson et al⁴¹ compared these four groups and found that PC had no effect on infant outcome in women who did not use drugs prenatally but had a beneficial effect on offspring of women who did use drugs during pregnancy. Thus, it is important to separate the effects of prenatal substance use from the effects of PC when evaluating infant outcomes.

This is a report from a prospective, longitudinal study of cocaine and crack use during pregnancy. This study assesses the effects of cocaine and crack use during each trimester of pregnancy on growth, morphology, behavior, and developmental status from birth through 7 years of age. Methodologic strengths of this study include 1) enrollment of two samples, the first is a sample of women, some of whom used cocaine and crack, who represent a general population from a large prenatal clinic; and the second is a sample of women who received NPC and were identified at delivery; 2) the use of a detailed confidential interview to assess the quantity, frequency, and pattern of cocaine, crack, alcohol, mar-

ijuana, tobacco, and other drug use for each trimester of pregnancy; and 3) collection of data regarding demographic factors, medical history, and lifestyle characteristics of the women, thus allowing for control of the covariates of cocaine use. This paper presents the effects of prenatal cocaine use on the neonatal growth of offspring of women who did and who did not receive PC. This paper uses the completed samples; an earlier report used preliminary data from the PC sample.⁴²

METHOD

Study Design

PC Sample

Women ≥ 18 years of age attending the PC clinic at Magee-Womens Hospital from March 1988 through December 1992 were eligible to participate in the PC cohort. Women were approached for interview during their fourth or fifth prenatal month visit. Women were not enrolled in this cohort if they came in for their first prenatal visit after the fifth month. No information was obtained from the medical charts about a woman's drug use before she was asked to participate in the study. Written consent was obtained according to the guidelines established by the Institutional Review Board of the University of Pittsburgh and by the Research Review and Human Experimentation Committee of Magee-Womens Hospital. A certificate of confidentiality, obtained from the Department of Health and Human Services, assured participants that their responses could not be subpoenaed.

All women who reported any cocaine or crack use during the first trimester were enrolled in the study. The next woman interviewed who reported no cocaine or crack use during pregnancy or during the year before pregnancy was also enrolled. This method of sampling resulted in the inclusion of women with a range of cocaine and crack use, thus enabling examination of dose-response relationships between exposure and outcome. Of those women eligible to be interviewed, 90% consented to participate in the study. Of the women interviewed, 320 met the inclusion criteria and were selected for the study. Women were interviewed again during their seventh prenatal month and in-hospital after delivery. Each interview assessed substance use for the preceding trimester as well as sociodemographic and lifestyle characteristics, social support, and psychologic characteristics of the women.

NPC Sample

A separate sample of women with little or NPC was enrolled from August 1991 through June 1993. There were two primary reasons for recruiting the NPC sample: 1) to recruit a sample of women who used cocaine heavily throughout pregnancy and 2) to investigate the effect of cocaine use in a sample with NPC to provide a comparison with other studies in the literature. Women were identified at delivery by the project nurse clinicians. Based on information contained in the medical records, the project nurses calculated whether a woman had inadequate or NPC according to Kessner's Prenatal Care Index.⁴³ Kessner's Prenatal Care Index is based on GA at the first prenatal visit, the total number of prenatal visits, and the GA at delivery. Inadequate care is defined as PC which began at ≥ 28 weeks and by the number of visits relative to GA (eg, ≤ 4 visits when GA is ≥ 34 weeks). Any woman with inadequate or NPC was approached to participate in the study.

Written consent for the NPC cohort was obtained according to the guidelines established by the Institutional Review Board of the University of Pittsburgh and by the Research Review and the Human Experimentation Committee of Magee-Womens Hospital. Of those women eligible to be interviewed, 83% consented to participate in the study. Women were interviewed after delivery with a composite interview that ascertained the same information as the three interviews that the PC sample received.

Sample Characteristics

PC Sample

Of the 320 women selected for the study, 17 became ineligible for participation because of abortion ($n = 1$), miscarriage ($n = 3$),

infant death ($n = 1$), home delivery ($n = 1$), or moving out of the area ($n = 11$). Of the remaining 303 eligible women, 1 was lost to follow-up and 2 refused to continue participation. Therefore, delivery assessments were completed on 300 mothers, representing 99% of the eligible sample. Four pairs of twins and 1 child with Trisomy 21 were excluded from the analysis, resulting in a final sample of 295 women and infants. The characteristics of the women and infants in the PC sample are presented in Table 1.

NPC Sample

A total of 99 women were selected for the study. One pair of twins was excluded from the analysis, resulting in a final sample of 98 women and infants. The characteristics of the women and infants in the NPC sample are presented in Table 1.

Measurement of Cocaine and Other Substance Use

Maternal use of cocaine and crack, as well as tobacco, alcohol, marijuana, and other illicit drugs, was assessed during detailed confidential interviewing. Interviewers were selected for their ability to discuss drug use comfortably and to identify accurately all drugs used, either by name, street name, or appearance. Because previous experience taught us that women were more willing to be honest about illicit drug use if they were not asked to report on current use, we asked about prepregnancy and first trimester use at the fourth month visit, second trimester use at the seventh month visit, and third trimester use after delivery for the PC sample. The NPC sample was asked about first, second, and third trimester substance use at delivery. For each substance, questions were asked first about usual quantity and frequency of use, followed by questions about maximum and minimum quantity and frequency. This information contributed to the calculation of an average daily use.

To increase the accuracy of reporting first trimester use, women were asked about their use during the periods from conception to their recognition of the pregnancy and from recognition to diagnosis of the pregnancy. Women often do not change their substance use patterns until after they have confirmed their pregnancy, which may not occur until late in the first trimester. However, they frequently report that their pattern of use after they knew they were pregnant was similar to their pattern of use for the entire first trimester. Therefore, we asked whether their use between these different periods was more like prepregnancy use or more like first trimester use. This allowed calculation of substance use during each month of the first trimester and a weighted estimate of the average daily use for the first trimester. This interview technique has been used in our previous studies of prenatal alcohol and marijuana use.⁴⁵

We did not use laboratory tests to detect cocaine. The most commonly used laboratory measure, urine screening, reflects use

only over a short period of time.^{46,47} The reliability and validity of meconium and hair analyses had not been established when this study was designed in the late 1980s, but these laboratory measures do not give an estimate of the pattern of use. This information is critical when evaluating the effect of a potential teratogen. Interviewing was the method of choice to collect detailed information regarding the timing and pattern of cocaine use, especially during the first trimester. However, we have taken two approaches to evaluate the comparability of our self-report data and biologic measures of cocaine use.

First, we accessed the medical record data for the women who were screened for clinical purposes; this allowed us to compare the urine screen results with our interview data. In the PC sample, 18% of the women had been screened by the hospital, and 44% of these women were positive for cocaine. All the women who had a positive urine screen for cocaine were identified by our study interview as users. In contrast, 48% of the women who told us they used cocaine, and who were screened, had a negative screen. Women who had a positive screen reported significantly more cocaine use during the second and third trimesters than did women with a negative screen. In the NPC sample, 91% of the sample had been screened by the hospital, and 62% of these women screened positive. Of the women who had a positive urine screen for cocaine, 85% were identified by our study interview as users. Thus, 15% were misreporters. In addition, 13% of the women who told us they used cocaine, and who were screened, had a negative screen. Women who had a positive screen reported significantly more cocaine use during the third trimester than did women with a negative screen. These data demonstrate that drug use information can be obtained reliably when interviews are well-constructed and when interviewers are selected and trained carefully.

The second approach was to describe the characteristics of the women in the NPC sample who were misreporters and to determine whether excluding them from the analyses affected the pattern of results. Women were defined as misreporters if they denied using cocaine/crack during all three trimesters, but had a positive urine screen at any time. The women who misreported ($n = 8$) did not differ from those who did not misreport ($n = 81$) in education, marital status, age, race, or hostility score. They also did not differ in the mean level of first, second, or third trimester alcohol, tobacco, marijuana, or other illicit drug use (excluding cocaine). The regression and group analyses for the NPC cohort were performed including and excluding the misreporters to determine their influence on the findings. The results did not change when the misreporters were excluded from the analyses.

Infant Outcome Measures

Infants were examined generally within 24 to 48 hours postdelivery by a pediatric nurse trained for the study protocol by the project pediatrician. The examiner was blind to maternal substance use status. The infant's crown-to-heel length and head circumference were measured. GA was assessed according to the Ballard et al⁴⁸ modification of the Dubowitz assessment. After the physical examination was completed, birth weight and Apgar scores were abstracted from the medical chart by study nurses, along with information on pregnancy, labor, and delivery complications. Pregnancy, labor, and delivery conditions were classified using common obstetric complication schemes as guidelines.⁴⁹⁻⁵¹ For example, pregnancy conditions included anemia, maternal infections, hypertension, and abnormal bleeding; labor conditions included precipitous labor, induction, pitocin augmentation, and premature labor; and delivery conditions included anesthesia, meconium stained fluid, infant resuscitation, nuchal cord, caesarean section, and forceps delivery.

Statistical Methods

Cocaine and crack use was converted into gram equivalents. One line was estimated as 1/30th (0.03) of a gram; one rock of crack was estimated to be equivalent to 0.2 g. These estimates were based on information obtained from toxicology laboratories and law enforcement officials in Pittsburgh, Pennsylvania. Cocaine/crack use was then expressed as average grams per day. For the PC sample analyses, first trimester cocaine use was treated as both a continuous and a dichotomous variable (use/no use). Second and third trimester use were treated as dichotomous variables because of the low frequency of second and third trimester users.

TABLE 1. Sample Characteristics

	PC Sample (N = 295)	NPC Sample (N = 98)
Maternal age (y)	24.8 (18–41)	25.5 (18–40)
Education (y)	11.9 (9–16)	11.4 (7–16)
% White	52	19
% Married at delivery	23	5
Median family income (\$)	450/mo	402/mo
Gravidity (mean)	3.1 (1–14)	4.3 (1–10)
% Primigravida	25	5
Parity (mean)	2.0 (1–7)	3.5 (1–8)
% Primiparous	43	9
% At least one miscarriage	26	22
% At least one abortion	37	31
Weight gain (lbs)	32.8 (–23–81)	21.6 (–29–50)
% Adequate PC*	46	0
% Male infants	54	51
GA (wk)	39.7 (26–44)	37.9 (27–43)
Birth weight (g)	3254 (930–5600)	2778 (846–3906)
% Premature (<37 wk)	7	26
% LBW (<2500 g)	9	23.5
% SGA†	10	20

* Kessner's Prenatal Care Index.⁴³

† Brenner et al.⁴⁴

For the NPC sample analyses, cocaine/crack use was treated as a continuous variable for each of the three trimesters because of the greater percentage of users in the NPC sample. The alcohol and marijuana variables were calculated as average number of drinks and joints per day, respectively, and the tobacco variable was calculated as the number of cigarettes per day. These variables were ascertained separately for each trimester.

Stepwise multiple regression models were used to assess the effects of prenatal cocaine/crack use on birth weight, length, and head circumference. Logistic regression models were used for the dichotomous outcomes of LBW (<2500 g vs ≥2500 g), small-for-gestational age (SGA) versus not SGA, according to the standards of Brenner et al,⁴⁴ and prematurity (<37 weeks vs ≥37 weeks). Potential confounds were selected based on theoretical and empirical considerations. Variables included in the regressions were cocaine, alcohol, marijuana, tobacco, and other drug use; infant gender and GA; maternal race, height, age, education, marital status, gravidity, weight gain during pregnancy, adequacy of PC (for the PC cohort only; 0 = adequate; 1 = intermediate; 2 = inadequate), and presence/absence of gestational diabetes. Because this is a study of the effects of a potential teratogen, analyses were performed separately for each trimester. In the analysis of the effects of first trimester cocaine/crack use, first trimester alcohol, tobacco, and marijuana use were controlled in the regression. Likewise, for analyses of second and third trimester effects, other substances used in those corresponding periods were controlled.

The regression models were tested for violation of assumptions. Residuals, Mahalanobis distance, and a modified Cook's statistic were used to identify outliers and influential points.⁵² The variables were also checked for adequacy of the tolerances. Tolerance is a measure of intercorrelation of predictors with small values indicating multicollinearity.

Group analyses were also conducted to investigate the effects of multiple drug use and of cocaine/crack use by level of PC. Significant covariates from the stepwise regression models were used in the analyses of covariance.

RESULTS

Descriptive Analyses

The prevalence of cocaine/crack use in the PC and NPC samples is presented in Table 2. For descriptive purposes, women who reported using one or more lines per day of powder cocaine or the equivalent in crack were classified as frequent users. Women who reported using less than one line of cocaine per day (or the equivalent in crack) were classified as occasional users. In the PC sample, during the year before pregnancy, 22% of women were frequent users of cocaine. When we used the information from the interview about cocaine use during the early part of the first trimester, before pregnancy recognition, 18.6% of the women were calculated to be frequent users. In the second and third trimesters, 4.5% and 6.2% were frequent users, respectively. The mean

level of cocaine use for the women who used during the first trimester was 0.23 g/day, or ~8 lines/day. Of the women who used during the first trimester, 50% reported snorting powder cocaine only, whereas the rest smoked crack. During the second and third trimesters, the mean level of use for the users was 0.17 g/day (~6 lines/day) and 0.14 g/day (~5 lines/day), respectively. Of the women who used during the third trimester, 20% reported snorting powder cocaine only and the rest smoked crack.

In the NPC sample, during the year before pregnancy, 41.8% of women were frequent users of cocaine/crack. During the first trimester, 40.8% were frequent users (Table 2). In the second and third trimesters, 35.7% and 34% were frequent users, respectively. The mean level of use for the women who used during the first trimester was 0.64 g/day (~3 rocks/day or 21 lines/day). Of the women in the NPC sample who used during the first trimester, 98% reported smoking crack. During the second and third trimesters, the mean level of use for the users was 0.74 g/day (~3.5 rocks/day or 25 lines/day) and 0.72 g/day (~3.5 rocks/day or 24 lines/day), respectively. Of the women who used during the third trimester, 98% smoked crack. Because of the small number of women who were occasional users in the NPC cohort, descriptive analyses will be presented for nonusers versus users for the NPC sample.

Table 3 presents the pattern of other drug use associated with cocaine/crack use in the PC and NPC samples. In the PC sample, women who were frequent users of cocaine during the first trimester were significantly more likely to use alcohol, marijuana, tobacco, and illicit drugs other than cocaine compared with women who did not use cocaine during the first trimester. The frequent cocaine users also used both alcohol and marijuana more heavily than did the women who did not use cocaine. During the third trimester, women in the PC sample who used cocaine were also more likely to use alcohol, tobacco, marijuana, and other illicit drugs than were women who did not use cocaine.

In the NPC sample, women who used cocaine/crack during the first trimester were significantly more likely to use alcohol more heavily than were women who did not use cocaine. During the third trimester, women who used cocaine were significantly more likely to use alcohol and marijuana than were women who did not use cocaine.

Comparing the two samples, the women who used cocaine in the NPC sample drank more alcohol during the first trimester compared with the women who used cocaine in the PC sample (3 vs 1.9 drinks/day; $P < .01$). The women who did not use cocaine during the first trimester in the NPC sample drank more alcohol (1.1 vs 0.4 drinks/day; $P < .05$), used more marijuana (0.4 vs 0.1 joints/day; $P < .05$), and were more likely to be cigarette smokers (74 vs 45%; $P < .001$) than were women who did not use cocaine in the PC sample.

The demographic and obstetric characteristics associated with first trimester cocaine/crack use in the PC and NPC samples are shown in Table 4. In the PC

TABLE 2. Prevalence of Cocaine Use Over Time (%)

	Level of Cocaine Use		
	None	Occasional*	Frequent†
PC sample (N = 295)			
Year before pregnancy	54.2	23.7	22.0
First trimester (calculated)	57.6	23.7	18.6
Second trimester	92.5	3.0	4.5
Third trimester	89.7	4.1	6.2
NPC sample (N = 98)			
Year before pregnancy	49.0	9.2	41.8
First trimester (calculated)	52.0	7.1	40.8
Second trimester	57.1	7.1	35.7
Third trimester	52.6	13.4	34.0

* Occasional, <1 line/day.

† Frequent, ≥1 line/day of cocaine or gram equivalent of crack.

TABLE 3. First Trimester Use of Other Drugs by Level of First Trimester Cocaine Use

	PC Sample			NPC Sample	
	No Cocaine Use <i>n</i> = 170	Occasional Use† <i>n</i> = 70	Frequent Use‡ <i>n</i> = 55	No Cocaine Use <i>n</i> = 51	Cocaine Use§ <i>n</i> = 47
Alcohol					
Number of drinks/d	0.4	1.6	2.2***	1.1	3.0**
% Drink	55.3	91.2	87.3***	84.3	80.8
% Drink ≥1 drink/d	11.2	48.5	54.6***	29.4	59.6**
Marijuana					
Number of joints/d	0.1	0.4	0.7***	0.44	0.52
% Smoke	17.1	54.4	60.0***	41.2	51.1
% Smoke ≥1 joint/d	4.1	16.2	18.2***	9.8	17.0
Tobacco					
Number of cigarettes/d	6.5	9.6	10.9**	8.3	10.8
% Smoke	44.7	69.1	83.6***	74.0	89.4
% Smoke ≥1 pack/d	16.5	22.1	21.8	14.0	23.4
Other drugs (excluding cocaine)¶					
% Use	3.5	10.3	12.7*	5.9	6.4

* $P < .05$; ** $P < .01$; and *** $P < .001$. Significance levels are for comparisons among the 3 PC groups and between the 2 NPC groups.

† Occasional, <1 line/day.

‡ Frequent, ≥1 line/day of cocaine or gram equivalent of crack.

§ Use, any use of cocaine or crack.

¶ For example, amphetamines, barbiturates.

sample, first trimester frequent users were older, more likely to be black, unmarried, and had lower family incomes than were women who were occasional or nonusers during the first trimester. In addition, the first trimester frequent users had higher gravidity and parity, a higher percentage reported at least one abortion, they weighed less before pregnancy, and had more complications during pregnancy than did the nonusers. The frequent users came in later for PC, had fewer prenatal visits, and had less adequate PC than did the nonusers. The groups did not differ in weight gain during pregnancy or in the number of labor or delivery complications. Third trimester cocaine users differed from

third trimester nonusers in these same characteristics.

In the NPC sample, women who used cocaine/crack during the first trimester were older and were more likely to have family incomes <\$500/month compared with nonusers. The women who used cocaine during the first trimester had higher gravidity, fewer were primiparous, a greater percentage reported having at least one abortion, they gained less weight during pregnancy, and they had more delivery conditions than did women who were nonusers during the first trimester. These characteristics also significantly differentiated third trimester cocaine users from nonusers in the NPC sample. There were

TABLE 4. Maternal Characteristics by Level of First Trimester Cocaine Use

	PC Sample			NPC Sample	
	No Cocaine Use <i>n</i> = 170	Occasional Use† <i>n</i> = 70	Frequent Use‡ <i>n</i> = 55	No Cocaine Use <i>n</i> = 51	Cocaine Use§ <i>n</i> = 47
Age (y)	23.9	25.0	27.4***	23.5	27.5***
% White	58.3	55.7	29.6**	25.5	12.8
Education (y)	12.0	11.8	11.9	11.4	11.4
% Married	27.6	14.3	11.1**	2.0	8.5
Family income (\$/mo)	746	625	475*	504	435
Income <\$500/mo (%)	41.1	60.9	66.0***	61.2	80.9*
Gravidity	2.7	3.3	4.2***	3.9	4.8*
% Primigravida	30.0	22.8	13.0*	7.8	2.1
Parity	1.9	2.1	2.4*	3.3	3.8
% Primiparous	48.2	42.9	25.9*	15.7	2.1*
% At least one abortion	28.2	42.9	59.3***	19.6	42.5*
Prepregnancy weight (lbs)	148	131	140**	139	133
Weight gain (lbs)	32.6	33.0	33.4	24.6	17.9*
GA first prenatal visit (wk)	13.2	14.7	15.0*	—	—
Total number of prenatal visits	10.6	9.7	8.4***	0.8	1.1
% Adequate prenatal care¶	54.7	44.3	23.6***	—	—
Pregnancy conditions	2.1	2.4	3.5***	2.7	3.1
Labor conditions	0.9	0.8	1.0	1.1	1.2
Delivery conditions	2.1	2.0	2.2	1.9	2.5*

* $P < .05$; ** $P < .01$; and *** $P < .001$. Significance levels are for comparisons among the 3 PC groups and between the 2 NPC groups.

† Occasional, <1 line/day.

‡ Frequent, ≥1 line/day of cocaine or gram equivalent of crack.

§ Use, any use of cocaine or crack.

¶ Kessner et al.⁴³

no differences between the two groups in race, marital status, or number of pregnancy or labor complications.

Comparing the samples, the women in the NPC sample were more likely to be black, less educated, gained less weight during pregnancy, and had higher gravidity and parity than did the women in the PC sample, regardless of cocaine use. The women in the NPC sample who did not use cocaine were more likely to be single and to have a lower family income than were women who did not use in the PC sample.

The characteristics of the infants in the PC and NPC samples are presented in Table 5. These values are not adjusted for any of the covariates of cocaine/crack use. In the PC sample, infants of first trimester frequent users had significantly lower mean GA, birth weight, length, and head circumference than did infants of nonusers. The infants of women who used cocaine frequently during the first trimester were also more likely to be LBW and premature. Women who used cocaine during the second trimester had infants with lower mean birth weight, length, and head circumference. Third trimester cocaine/crack use was associated with lower birth weights in the PC sample.

In the NPC sample, infants of first trimester cocaine/crack users were significantly shorter and had an increased incidence of SGA compared with the infants of nonusers. Infants of women who used cocaine/crack during the second trimester had lower mean birth weight, length, and head circumference, and an increased incidence of SGA and LBW. Third trimester cocaine/crack use was associated with lower birth weight, length, head circumference, and an increased rate of LBW.

Across samples, the offspring of women in the NPC sample had reduced GA, birth weight, length, and head circumference, and an increased incidence of prematurity compared with the offspring of the PC sample, regardless of cocaine use. The offspring of women who used cocaine in the NPC sample had an increased incidence of LBW and SGA compared with the offspring of women who used cocaine in the PC sample.

Regression Analyses

Regression analyses were used to control for the covariates described previously (Table 6). In the PC sample, when all the covariates were considered, cocaine/crack use during the first trimester was associated with reduced GA. Cocaine use during the second trimester predicted reduced birth weight and length. There were no significant effects of cocaine/crack use during the third trimester. Growth was also predicted by race, maternal height, weight gain during pregnancy, the presence of diabetes, adequacy of PC, GA, infant gender, and prenatal alcohol and tobacco use. The amount of variance explained by the regression models ranged from 37% to 54% for the growth outcomes and from 8% to 14% for GA.

In the NPC sample, cocaine/crack use during the first and second trimesters significantly predicted decreased birth weight, length, head circumference, and an increased incidence of SGA infants. Third trimester cocaine/crack use was associated significantly with decreased weight and an increased incidence of LBW, SGA, and prematurity. These findings remained significant when the misreporters were removed from the analyses. Neonatal growth in the NPC sample was also predicted by maternal height, weight gain during pregnancy, the presence of diabetes, GA, and prenatal alcohol, tobacco, marijuana, and other illicit drug use. The amount of variance explained by the regression models ranged from 38% to 57% for the growth outcomes and from 9% to 13% for GA.

Group Analyses

The effects of multiple drug use were explored by creating a typology. Three groups were defined for each trimester: 1) women who did not use alcohol, marijuana, or cocaine; 2) women who did not use cocaine but did use alcohol and/or marijuana at least three times per week (this cutoff was used to make Groups 2 and 3 comparable with respect to the level of alcohol and marijuana use); 3) women who used cocaine, alcohol, and/or marijuana. In the PC sample, the offspring of women who used cocaine, alcohol, and marijuana during the second trimester were significantly smaller in weight, length, and head circumference than were the offspring of women who

TABLE 5. Infant Characteristics by Level of First Trimester Cocaine Use†

	PC Sample			NPC Sample	
	No Cocaine Use <i>n</i> = 170	Occasional Use‡ <i>n</i> = 70	Frequent Use§ <i>n</i> = 55	No Cocaine Use <i>n</i> = 51	Cocaine Use¶ <i>n</i> = 47
GA (wk)	40.0	39.6	39.0**	38.0	37.9
Weight (g)	3362	3216	3007***	2867	2681
Length (cm)	50.0	49.5	48.9*	48.5	47.4*
Head circumference (cm)	34.7	34.3	33.9**	33.4	33.1
% LBW	5.4	8.6	20.0***	15.7	31.9
% SGA	9.0	5.7	16.4	7.8	34.0*
% Premature	3.6	8.6	14.6*	25.5	25.5

* $P < .05$; ** $P < .01$; and *** $P < .001$. Significance levels are for comparisons among the 3 PC groups and between the 2 NPC groups.

† Data are not adjusted for significant covariates.

‡ Occasional, <1 line/day.

§ Frequent, ≥ 1 line/day of cocaine or gram equivalent of crack.

¶ Use, any use of cocaine or crack.

TABLE 6. Regression Analyses

Variables in the Model	Significant Outcomes	
	PC Sample	NPC Sample
Prenatal substance use		
Cocaine	Time 1: GA Time 2: wt, lt, hc*	Time 1: wt, lt, hc, SGA Time 2: wt, lt, hc, SGA Time 3: wt, LBW, SGA, prem
Alcohol	Time 1: GA, LBW, prem Time 2: lt, hc, prem Time 3: lt, GA, prem	Time 1: lt Time 2: LBW
Tobacco	Time 1, 2, 3: wt, lt, hc, LBW, SGA	Time 1, 2, 3: hc
Marijuana	—	Time 1: GA, LBW; Time 2: lt
Other illicit drugs	—	Time 1: wt, hc
Maternal variables		
Age	—	lt
Race	wt, lt, hc, SGA	prem
Education	—	lt
Marital status	GA	
Height	wt, lt, hc	lt, hc, LBW
Gravidity	GA	—
Weight gain during pregnancy	wt, lt, hc, LBW, SGA	wt, lt, hc, LBW, SGA
Diabetes	wt, lt, hc	wt, lt, hc
Adequacy of PC	wt, lt, hc, GA, LBW, prem	—
Infant variables		
GA	wt, lt, hc	wt, lt, hc
Gender	wt, lt, hc	lt

* With second trimester alcohol removed.

Time 1 indicates first trimester; time 2, second trimester; time 3, third trimester; wt, weight; lt, length; hc, head circumference; prem, premature (≤ 37 weeks).

did not use drugs during the second trimester, after adjusting for covariates (Table 7). The offspring of women who used alcohol and marijuana were intermediate in birth weight, length, and head circumference between the offspring of groups 1 and 3. For the NPC sample, there was an insufficient number of women in group 1 for the first trimester and in group 2 for the second and third trimesters to conduct this analysis.

The two samples were analyzed together to explore the combined effects of cocaine/crack use and the level of PC. Four groups were defined: PC/no cocaine use; PC/cocaine use; NPC/no cocaine use; and NPC/cocaine use (Table 8). There were significant differences between the PC/no cocaine and PC/cocaine groups in birth weight, length, and head circumference, as was found in the regression anal-

yses for second trimester use. Within the NPC group, the infants exposed to cocaine during the second trimester were significantly smaller in length and head circumference and were more likely to be SGA than were the nonexposed infants. These results also parallel the regression findings for second trimester use.

In comparisons across the samples, the infants of the NPC/cocaine use group were significantly smaller in birth weight, length, and head circumference, and had higher rates of prematurity, LBW, and SGA than did the infants of the PC/no cocaine use group. There were no significant differences between the PC/cocaine use and NPC/cocaine use infants. The offspring of the PC/no cocaine use and NPC/no cocaine use groups differed only in the rate of prematurity. The infants of the PC/cocaine use group

TABLE 7. Effects of Multiple Drug Use: Prenatal Care Sample

	Group 1†	Group 2‡	Group 3§	Significance
Birth weight¶ (g)				
First trimester	3202	3287	3227	NS
Second trimester	3311	3230	3101	1 vs 3*
Third trimester	3264	3224	3190	NS
Length¶ (cm)				
First trimester	49.6	49.7	49.6	NS
Second trimester	49.9	49.8	48.4	1 vs 3***; 2 vs 3**
Third trimester	49.8	49.1	49.2	NS
Head circumference¶ (cm)				
First trimester	34.4	34.6	34.4	NS
Second trimester	34.7	34.4	34.0	1 vs 3**
Third trimester	34.6	34.4	34.6	NS

* $P < .10$; ** $P < .05$; and *** $P < .01$. Numbers for groups 1, 2, 3: first trimester: 71, 35, 119, respectively; second trimester: 134, 32, 17, respectively; and third trimester: 150, 24, 23, respectively.

† No alcohol, marijuana, or cocaine use.

‡ No cocaine use and alcohol and/or marijuana use ≥ 3 times/week.

§ Cocaine use and alcohol and/or marijuana use.

¶ Adjusted for race, gender, GA, maternal height, first trimester tobacco use, and weight gain during pregnancy.

TABLE 8. Combined Effects of PC and Second Trimester Cocaine Use

	PC/No Cocaine (Group 1) <i>n</i> = 246	PC/Cocaine (Group 2) <i>n</i> = 20	NPC/No Cocaine (Group 3) <i>n</i> = 56	NPC/Cocaine (Group 4) <i>n</i> = 42	Significance
Birth weight* (g)	3187	2985	3134	3002	1 vs 2‡; 1 vs 4‡
Length* (cm)	49.5	48.3	49.4	48.6	1 vs 2§; 2 vs 3‡; 3 vs 4‡; 1 vs 4‡
Head circumference* (cm)	34.3	33.8	34.2	33.7	1 vs 2‡; 3 vs 4‡; 1 vs 4§
Premature† (%)	5	5	24	30	1 vs 3§; 1 vs 4§
LBW† (%)	7	15	15	35	1 vs 4§
SGA† (%)	8	20	11	33	1 vs 4‡; 3 vs 4‡

* ANCOVA adjusted for race, gender, GA, maternal height, second trimester tobacco use, and weight gain during pregnancy.

† Logistic regression adjusted for race, gravidity, weight gain during pregnancy, second trimester alcohol, and cigarette use.

‡ *P* < .05.

§ *P* < .01.

were shorter than were the infants of the NPC/no cocaine use group, but there were no other significant differences.

DISCUSSION

This is a unique, prospective study of the effects of prenatal cocaine use on neonatal growth in two samples of women, one with and one without PC. The same assessment and interviewing methods were used in both samples. These two samples shared some characteristics. In both samples, the women who used cocaine were older, had lower family incomes, and used more alcohol prenatally. However, the women who did not use cocaine in the NPC sample used other drugs more heavily than did the women who did not use cocaine in the PC sample. In addition, the women in the NPC sample continued their cocaine use throughout pregnancy, used crack almost exclusively, and were more likely to be black compared with the PC sample. These factors are important determinants of neonatal growth, and therefore it is crucial to control for these characteristics to avoid biases associated with use or nonuse of PC.

In the PC sample, there were significant effects of second trimester cocaine/crack use on birth weight, length, and head circumference. In the NPC cohort, there were significant effects of first and second trimester cocaine/crack use on birth weight, length, head circumference, and the proportion of infants who were SGA. Each of these effects of cocaine/crack remained significant after controlling for prenatal use of alcohol, tobacco, marijuana, and other illicit drugs, for infant gender and GA, and for maternal factors, such as race, age, education, height, weight gain during pregnancy, diabetes, and the adequacy of PC (in the PC cohort). These effects were consistent in both the regression and group analyses.

The effect of cocaine/crack use on growth was associated with exposure during the first and second trimesters of pregnancy. In both samples, each of the growth parameters was affected, indicating symmetric growth retardation. This pattern of effects is consistent with literature indicating that symmetric growth retardation is caused by insults during the first two thirds of pregnancy.^{53,54} The finding of neonatal growth deficits resulting from prenatal cocaine exposure, after controlling for potential confounding

variables, is comparable to reports from other longitudinal studies.^{5,7,55}

Across samples, women who did not have PC and who used cocaine differed in every outcome from the women who had PC and who did not use cocaine. This replicates findings from several studies.^{37,41} However, the two groups differed in a number of sociodemographic and substance use characteristics that in themselves lead to poorer pregnancy outcome. We have argued that the failure to account for these differences might explain some of the negative effects that have been attributed to prenatal cocaine exposure.²⁸ These analyses allowed us to begin to address this question.

Within both samples, infants exposed to cocaine were significantly smaller compared with infants who were not exposed to cocaine. In the PC sample, this was true even after controlling for the adequacy of PC. Across samples, there were no significant differences in the outcomes of infants exposed to cocaine in the PC compared with those exposed to cocaine in the NPC sample. Therefore, the adequacy of PC was not a significant factor in determining the differences between cocaine-exposed and nonexposed infants. Moreover, given the similarity in outcomes related to cocaine exposure between the two groups, it is likely that the significant differences are related to cocaine exposure and not to other covariates that might differentiate the two groups.

This study represents an improvement over previous studies because of its prospective design, large number of subjects, trimester-specific drug use information, and attempts to control for confounding factors in the analysis. Women enrolled in this project represent a community-based sample. They were not selected based on their involvement in drug treatment programs, as were cocaine users in some previous studies. All women in the PC sample received PC by their fifth month of pregnancy. We also tracked the number of visits and the adequacy of PC, thus allowing for control of the differing amount of PC by level of cocaine use. Women in the PC sample were interviewed at the same time points and at frequent intervals to minimize recall bias. The interview techniques have been used in several previous studies of substance use in pregnancy and have been shown to be reliable and valid.^{29,30,56}

A potential limitation of this study is that drug

screening was not used. Urine screening has been shown to identify some women who deny use on interview. However, it does not detect many other women who use cocaine during pregnancy. As we reported, our interview identified a much higher percentage of users than did the urine screen conducted by the hospital. A comparison of these two techniques demonstrated that our interview identified all the women in the PC sample who were positive on the urine screen. There were a small number of misreporters in the NPC sample. When the analyses were run including and excluding these women, the results did not change, indicating that these women did not bias the conclusions from the study. We also showed that women with positive urine screens were heavier users than were women with negative screens. Thus, reliance on urine screens to enroll a sample would result in a nonrepresentative sample of women who use cocaine during pregnancy. Detailed, confidential interviewing close to the time of the drug use remains an effective way to identify users and to characterize the quantity and pattern of cocaine use, as well as to obtain information about other substances such as alcohol, marijuana, and tobacco.²⁸

CONCLUSION

In summary, in this prospective study, cocaine/crack exposure during early pregnancy was significantly associated with symmetric growth retardation in a sample of women with PC and in a sample of women with NPC. These effects were significantly related to cocaine exposure after controlling for the covariates of cocaine use and for the adequacy of PC. Thus, prenatal cocaine exposure leads to intrauterine growth deficits. These cohorts are being followed throughout childhood to determine whether there are long-term effects of prenatal cocaine/crack exposure on growth.

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