

# Association Between Patterns of Maternal Substance Use and Infant Birth Weight, Length, and Head Circumference

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**ABSTRACT.** *Objective.* To determine the effects of patterns of drug use during term pregnancy on infant growth parameters at birth.

*Methods.* Histories of cocaine, opiate, alcohol, tobacco, and marijuana use during the 3-month period before pregnancy and the 3 trimesters of pregnancy were recorded at the infants' 1-month visit. Patterns of use were categorized as consistently high, moderate, or low/none or increasing/decreasing, and effects on growth parameters were analyzed in multivariate linear regression analyses, with adjustment for clinical site, maternal age, prepregnancy weight, multidrug use, and socioeconomic status.

*Results.* A total of 241 cocaine-exposed women and 410 non-cocaine-exposed women participated in the study. In the cocaine-exposed group, 75% used alcohol, 90% used tobacco, and 53% used marijuana; in the non-cocaine-exposed group, 57% used alcohol, 34% used tobacco, and 19% used marijuana. Birth weight, birth length, and head circumference were significantly greater among infants born to women who used no drugs, compared with women with any cocaine, opiate, alcohol, tobacco, or marijuana use, and were greater among infants born to cocaine nonusers, compared with cocaine users. With adjustment for confounders, birth weight was significantly affected by cocaine (deficit of 250 g with consistently low pattern) and tobacco (deficits of 232 g with consistently high pattern, 173 g with consistently moderate pattern, 153 g with decreasing pattern, and 103 g with consistently low pattern). Head size was affected by cocaine (deficit of 0.98 cm with consistently moderate pattern) and tobacco (deficits of 0.72 cm with consistently high pattern and 0.89 cm with consistently moderate pattern). Birth length was affected by tobacco use only (deficits of 0.82 cm with consistently high pattern and 0.98 cm with decreasing use).

*Conclusion.* Patterns of tobacco use during pregnancy affect birth weight, length, and head circumference, whereas cocaine affects birth weight and head size, when adjustments are made for confounders, including multidrug use. *Pediatrics* 2004;114:e226–e234. URL: <http://www.pediatrics.org/cgi/content/full/114/2/e226>; *prenatal, cocaine, alcohol, tobacco, marijuana, infant birth weight, length, head circumference.*

ABBREVIATIONS. MISU, Maternal Inventory of Substance Use.

Maternal cocaine use during pregnancy has been associated with decreased growth parameters at birth for infants.<sup>1–5</sup> Women who use cocaine during pregnancy are often exposed to many drugs, including alcohol and tobacco,<sup>1–6</sup> both of which have been shown to have effects on birth weight in studies evaluating the use of these substances alone or in combination.<sup>7–13</sup> The timing and amount of fetal exposure to cocaine, tobacco, and alcohol during pregnancy also have been noted to influence birth weight.<sup>2,10,11,14</sup> Infants born to women who stopped smoking had higher birth weights than did those born to women who reduced smoking or who did not change behavior.<sup>10,11</sup> Infants born to women who drank throughout pregnancy had smaller head sizes than did those born to women who stopped drinking in the second trimester or who did not drink during pregnancy.<sup>15</sup> The effects of changes in patterns of use of these drugs when they are used in combination needs to be explored.

The purpose of this study was to determine the effects of patterns of cocaine, alcohol, tobacco, and marijuana use during pregnancy on growth parameters at birth. The hypothesis of our study was that the birth weight, length, and head circumference of infants born to women who decreased or stopped the use of cocaine, alcohol, tobacco, or marijuana during pregnancy would be greater than those of infants born to women who used these substances continuously throughout pregnancy. Because cocaine use has been associated with preterm delivery, only term (38–42 weeks of gestation) pregnancies were evaluated for this study. We evaluated the effects of cocaine exposure while controlling for the level of multidrug exposure, as suggested in a recent systematic review.<sup>16</sup>

## METHODS

This analysis was conducted as part of a study evaluating the effects of maternal substance use during pregnancy on infant outcomes, performed in 4 centers of the National Institute of Child Health and Human Development Neonatal Research Network.<sup>5</sup> The 4 centers were Brown University (Providence, RI), University of Miami (Miami, FL), University of Tennessee (Memphis, TN), and Wayne State University (Detroit, MI). The study was approved by the institutional review board at each center.

Eligible women were approached in the hospital after delivery of their infants, and consent was obtained for study participation. Mothers of all infants with a birth weight of <1500 g were eligible, whereas mothers of infants with a birth weight of >1500 g were eligible during defined, center-specific, recruitment hours. Exclu-

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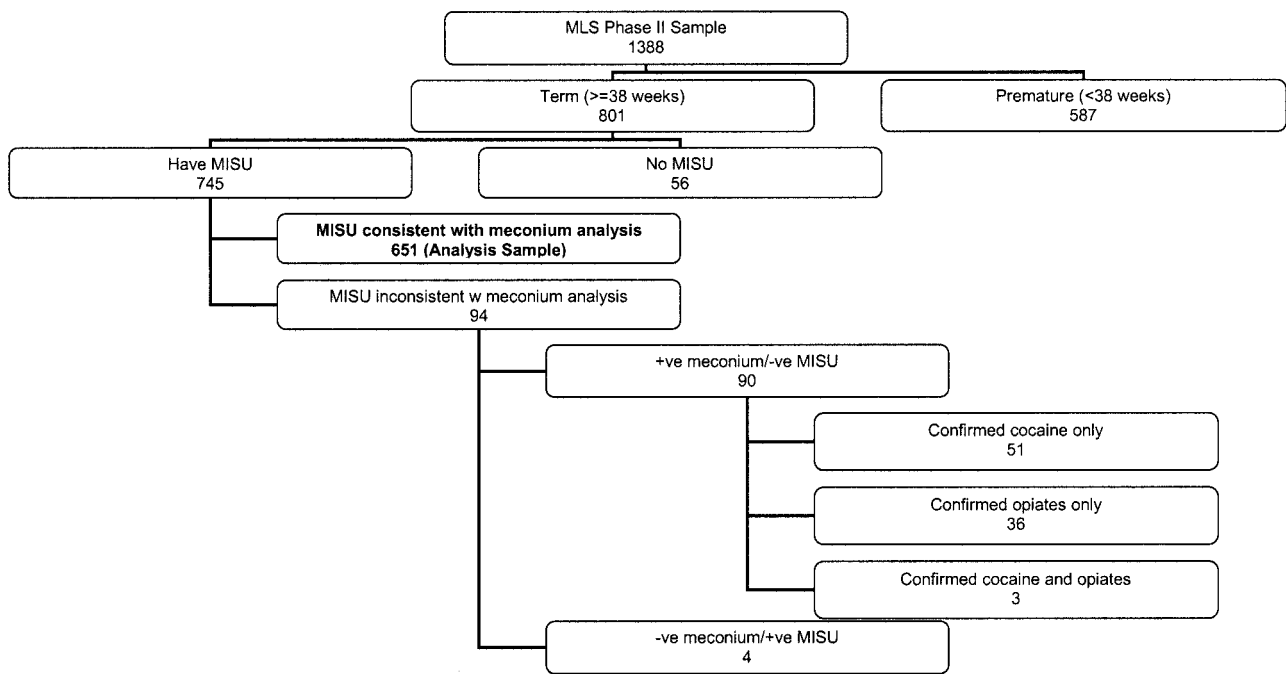


Fig 1. Flowchart for selection of study group.

sion criteria were birth outside the catchment area for follow-up monitoring, maternal age of <18 years, multiple gestation, or maternal psychosis. A detailed history of the pregnancy and delivery course was obtained by trained interviewers. The infants underwent physical and Ballard examinations, including head circumference and length measurements, performed by a trained research nurse. Gestational age was assessed with the Ballard examination. Meconium was collected for all study infants and sent to a central laboratory for analysis of metabolites of illicit drugs with the enzyme multiplied immunoassay technique, followed by gas chromatography/mass spectroscopy analysis of all positive samples.<sup>6,17</sup> Before discharge, maternal and infant charts were abstracted by the research nurse, using definitions from a manual of operations developed by the study investigators.

Maternal data recorded from hospital interviews and chart abstraction included prenatal care (defined as  $\geq 1$  prenatal visit), hospitalization, and medications during pregnancy and delivery. Infant data recorded from chart abstraction included the hospital course and the diagnosis at discharge from the neonatal unit.

At 1 month of age, 2 groups of infants were selected for evaluation for the neurodevelopmental outcome phase of the study, ie, a cohort that had been exposed to cocaine or opiates in utero and a group-matched comparison cohort that had not been exposed to cocaine or opiates. Because multidrug exposure is common among women who use illicit drugs, alcohol, nicotine, and marijuana exposure could occur in both cohorts. Exposure was defined on the basis of admitted (in the postpartum study interview) use of cocaine or opiates during pregnancy or an infant meconium sample that was confirmed positive, with gas chromatography/mass spectroscopy, for metabolites of cocaine or opiates. An infant was eligible for the comparison group only if the mother denied a history of cocaine or opiate use 3 months before and during the pregnancy and the infant's meconium sample was negative for metabolites, as assessed with the enzyme multiplied immunoassay technique. Comparison group infants were matched according to race, gender, and gestational age with each exposed infant at each site.

Use of cocaine, opiates, marijuana, alcohol, and tobacco during pregnancy was assessed with a detailed questionnaire administered at the 1-month clinic visit. This questionnaire, the Maternal Inventory of Substance Use (MISU), assessed drug use during 4 time periods, ie, 3 months before pregnancy and during the first, second, and third trimesters of pregnancy. The questionnaire was developed on the basis of self-reported tobacco use, which was well validated in a meta-analysis.<sup>18</sup> The questionnaire was administered only to biological mothers. Interviewers were trained and

certified in the recognition and identification of illicit drugs and in assisting recall of use by mothers with the use of calendars.

The frequency of use during the 4 time periods was categorized as high, moderate, low, or no use. For cocaine, high use was categorized as more often than 1 or 2 days/week, moderate use as 1 to 3 days/month, and low use as 1 or 2 days in 3 months. For alcohol, high use was defined as more often than 3 to 6 days/week or binge drinking (defined as 5 drinks at any 1 time), moderate use as 1 or 2 days/week or 1 to 3 days/month and no binge drinking, and low use as 1 or 2 days in 3 months and no binge drinking. Tobacco use during each time period of the pregnancy was categorized as high use of  $\geq 1$  pack/day (>20 cigarettes/day), moderate use of 0.5 to 1 pack/day (9–19 cigarettes/day), or low use of <0.5 pack/day (<9 cigarettes/day). Marijuana use was categorized as follows: high use was defined as 1 to  $\geq 3$  joints more often than 1 or 2 days/week or <1 joint every day, moderate use as >1 joint 1 to 3 days/month or <1 joint 1 to 2 days/week, and low use as <1 joint 1 to 3 days/month. The pregnancy was categorized into 2 periods; the early period was defined as the 3-month period before pregnancy and the first trimester, and the late period was defined as the second and third trimesters. Use within the early and late periods was based on the maximal use of each substance within the period (eg, if use was moderate in the second trimester and low in the third, use was categorized as moderate). The patterns of use were classified as consistently high use (high use in both the early and late periods), increasing use (increasing from the early period to the late period), consistently moderate use (moderate use in the early and late periods), decreasing use (decreasing from the early period to the late period), or consistently low use (low use in the early and late periods).

Demographic and clinical characteristics for the cocaine-exposed and comparison groups were initially compared in unadjusted analyses using *t* tests for continuous variables and  $\chi^2$  tests for categorical variables. The relationships between patterns of drug use and birth weight, length, and head circumference were analyzed in multivariate linear regression analyses in which the effects of patterns of use of cocaine, alcohol, marijuana, and tobacco during pregnancy on birth weight, length, and head circumference were compared with the effects of no substance use. The effects of patterns of exposure were evaluated for each substance, with adjustment for the following variables: patterns of use of the other 3 substances, clinical site, maternal race, maternal age, parity, prepregnancy weight,<sup>19</sup> gestational age (between 38 and 42 weeks), infant gender, and socioeconomic status, as measured with the Hollingshead index. Adjustments were also made for multiple comparisons (Tukey-Kramer test).

**TABLE 1.** Comparison of Subjects in Analysis Sample and Subjects Not in Analysis Sample

|                                    | In Sample<br>( <i>n</i> = 651) | Not in Sample<br>( <i>n</i> = 150) |
|------------------------------------|--------------------------------|------------------------------------|
| Cocaine exposure, %                | 37                             | 96*                                |
| Maternal age, y                    | 27.1 ± 5.7                     | 29.0 ± 6.1*                        |
| Prepregnancy weight, lb            | 149.1 ± 39.8                   | 140.7 ± 39.3*                      |
| Parity, no.                        | 3 ± 2                          | 4 ± 2*                             |
| Socioeconomic status†              | 29 ± 11                        | 28 ± 11                            |
| Gestational age, wk                | 39 ± 2                         | 39 ± 2                             |
| Black race, %                      | 77                             | 64*                                |
| White race, %                      | 14                             | 26*                                |
| More than high school education, % | 21                             | 21                                 |
| Sexually transmitted disease, %    | 26                             | 28                                 |
| Hospitalized, %                    | 18                             | 19                                 |
| Hypertension/preeclampsia, %       | 4                              | 2                                  |
| Diabetes mellitus, %               | 2                              | 1                                  |
| Other infections, %                | 34                             | 40                                 |
| Abruptio placenta, %               | 3                              | 0*                                 |

Data are presented as percentage and mean ± SD.

\* *P* < .05.

† Socioeconomic status was measured with the Hollingshead index.

## RESULTS

There were 801 mother-infant dyads, at 38 to 42 weeks of gestation, enrolled in the longitudinal phase of the study, which evaluated the effects of substance use during pregnancy on infant outcomes (Fig 1). The MISU was administered to 745 biological mothers, including 331 of 385 in the cocaine-exposed group and 414 of 416 in the comparison group (the remaining 56 women were not biological mothers). Within the MISU subset, 241 of 331 women in the exposed group responded with a positive history of any cocaine use during any of the 3 months before pregnancy and during the 3 trimesters of pregnancy; this included 23 women who used opiates in addition to cocaine. Ninety of the 331 exposed women denied a history of cocaine or opiate use; meconium analysis of their infants revealed cocaine metabolites for 51 infants, opiate metabolites for 36 infants, and cocaine and opiate metabolites for 3 infants. These 90 women were excluded, because patterns of drug use

could not be determined. Four women reported a history of cocaine use but meconium analysis revealed no metabolites; these women were also excluded. The 651 biological mothers who responded to the MISU and their term infants are the subjects of this report, including 241 cocaine-exposed and 410 non-cocaine-exposed dyads. When clinical and demographic characteristics of the 651 women in the analysis sample were compared with those of the 150 women not in the sample, women not in the analysis sample exhibited a higher incidence of cocaine use and were older. The educational status and rates of most pregnancy complications were similar for the women who were not sampled and those who were (Table 1).

Characteristics of the study subjects are shown in Table 2. Women in the cocaine-exposed group exhibited lower prepregnancy weights and were older than non-cocaine-exposed women. Exposed women had a lower socioeconomic status and educational level than did non-cocaine-exposed women. More women in the cocaine-exposed group had sexually transmitted diseases. More women in the cocaine-exposed group used alcohol (182 of 241 women, 75%), tobacco (218 of 241 women, 90%), and marijuana (127 of 241 women, 53%) than did women in the non-cocaine-exposed group (alcohol: 233 of 410 women, 57%; tobacco: 141 of 410 women, 34%; marijuana: 78 of 410 women, 19%; *P* < .05). More women in the cocaine-exposed group used alcohol, tobacco, and marijuana (99 of 241 women, 41%) than did women in the non-cocaine-exposed group (40 of 410 women, 10%).

The birth weight at term gestation among infants born to women who used cocaine during pregnancy (*n* = 241) was 2983.5 ± 481 g (mean ± SD), the length was 48.8 ± 2.7 cm, and the head circumference was 33.4 ± 1.8 cm. The average birth weight and length of the infants born to the 23 women who used cocaine and opiates during pregnancy were 2954 ± 545 g and 48.2 ± 3.2 cm, respectively, and the average head circumference was 33.3 ± 1.5 cm. Growth parameters

**TABLE 2.** Characteristics of Women in Cocaine-Exposed and Comparison Groups

|                                    | Cocaine-Exposed<br>( <i>n</i> = 241) | Non-Cocaine-Exposed<br>( <i>n</i> = 410) |
|------------------------------------|--------------------------------------|--|
| Maternal age, y                    | 29.5 ± 4.9                           | 25.7 ± 5.7*                              |
| Prepregnancy weight, lb            | 137.8 ± 31.7                         | 155.4 ± 42.4*                            |
| Parity, no.                        | 3 ± 2                                | 2 ± 2*                                   |
| Socioeconomic status†              | 27 ± 10                              | 29 ± 11*                                 |
| Gestational age, wk                | 38 ± 2                               | 39 ± 2*                                  |
| Black race, %                      | 78                                   | 76                                       |
| White race, %                      | 14                                   | 15                                       |
| More than high school education, % | 17                                   | 23*                                      |
| Sexually transmitted disease, %‡   | 35                                   | 21*                                      |
| Hospitalized, %                    | 18                                   | 18                                       |
| Hypertension/preeclampsia, %       | 3                                    | 5  |
| Diabetes mellitus, %               | 1                                    | 2  |
| Other infections, %                | 36                                   | 33                                       |
| Abruptio placenta, %               | 4                                    | 2  |

\* *P* < .05.

† Socioeconomic status was measured with the Hollingshead index.

‡ Including self-reports of any known sexually transmitted diseases, active genital herpetic lesions, syphilis, and gonorrhea.

**TABLE 3.** Association of Substance Use and Birth Weight, Birth Length, and Head Circumference in the Total Cohort ( $n = 651$ )

|  | No. | Birth Weight,<br>g* | Birth Length,<br>cm* | Head Circumference,<br>cm* |
|--|-----|---------------------|----------------------|----------------------------|
| Cocaine exposed ( $n = 241$ )            |     |                     |                      |                            |
| Cocaine only                             | 7   | 3317 ± 286          | 51.5 ± 2.2           | 34.8 ± 1.1                 |
| Cocaine and alcohol                      | 7   | 2964 ± 419          | 49.9 ± 1.7           | 33.6 ± 1.5                 |
| Cocaine and tobacco                      | 29  | 2958 ± 439          | 49.2 ± 2.7           | 33.6 ± 1.3                 |
| Cocaine and marijuana                    | 4   | 3548 ± 387          | 51.3 ± 2.1           | 34.1 ± 1.8                 |
| Cocaine, alcohol, and tobacco            | 71  | 2913 ± 471          | 48.4 ± 2.7           | 33.0 ± 2.3                 |
| Cocaine, alcohol, and marijuana          | 5   | 3546 ± 659          | 51.8 ± 4.0           | 34.1 ± 1.9                 |
| Cocaine, tobacco, and marijuana          | 19  | 3057 ± 412          | 49.2 ± 2.0           | 33.8 ± 1.7                 |
| Cocaine, alcohol, tobacco, and marijuana | 99  | 2954 ± 491          | 48.3 ± 2.7           | 33.3 ± 1.4                 |
| Non-cocaine exposed ( $n = 410$ )        |     |                     |                      |                            |
| No use                                   | 141 | 3266 ± 468          | 50.3 ± 2.5           | 34.0 ± 1.4                 |
| Alcohol only                             | 96  | 3312 ± 500          | 50.4 ± 2.2           | 34.1 ± 1.5                 |
| Tobacco only                             | 27  | 3204 ± 553          | 49.8 ± 2.8           | 33.6 ± 1.6                 |
| Marijuana only                           | 3   | 2949 ± 454          | 51.2 ± 4.2           | 34.0 ± 0.9                 |
| Alcohol and tobacco                      | 68  | 3113 ± 534          | 49.7 ± 2.5           | 33.9 ± 1.5                 |
| Alcohol and marijuana                    | 29  | 3232 ± 487          | 49.4 ± 3.1           | 34.1 ± 1.3                 |
| Tobacco and marijuana                    | 6   | 3397 ± 394          | 50.7 ± 1.2           | 34.3 ± 1.6                 |
| Alcohol, tobacco, and marijuana          | 40  | 3181 ± 565          | 49.8 ± 3.2           | 33.9 ± 1.8                 |

Birth weight, birth length, and head circumference of 141 infants not exposed to any substances were significantly higher than birth length, birth weight, and head circumference of all remaining infants (ie, those exposed to  $\geq 1$  substances).

\* Mean ± SD.

were higher among infants born to women who did not use cocaine during pregnancy ( $n = 410$ ), compared with infants exposed to cocaine, with a birth weight of  $3236 \pm 504$  g ( $P < .05$ ), length of  $50.1 \pm 2.6$  cm ( $P < .05$ ), and head circumference of  $34.0 \pm 1.5$  cm ( $P < .05$ ). The relationship of substance use to birth weight, length, and head circumference among cocaine-exposed ( $n = 241$ ) and non-cocaine-exposed ( $n = 410$ ) infants can be seen in Table 3. The birth

weight of infants born to the 141 women who used no drugs during pregnancy (no cocaine, opiates, alcohol, tobacco, or marijuana) was  $3266 \pm 468$  g, whereas that of infants born to women who used any cocaine, opiates, alcohol, tobacco, or marijuana was  $3109 \pm 517$  g ( $P < .05$ ). The head circumference of the infants born to the 141 women who used no drugs was  $34.0 \pm 1.4$  cm, whereas that of the remaining infants was  $33.7 \pm 1.7$  cm ( $P < .05$ ). The length of the

**TABLE 4.** Effects of Patterns of Drug Use During Pregnancy on Adjusted Mean Birth Weight, Birth Length, and Head Circumference

| Patterns of Use       | Cocaine-Exposed ( $n = 241$ ) |                     |                      |                            | Non-Cocaine-Exposed ( $n = 410$ ) |                     |                      |                            |
|-----------------------|-------------------------------|---------------------|----------------------|----------------------------|-----------------------------------|---------------------|----------------------|----------------------------|
|                       | No.                           | Birth Weight,<br>g* | Birth Length,<br>cm* | Head Circumference,<br>cm* | No.                               | Birth Weight,<br>g* | Birth Length,<br>cm* | Head Circumference,<br>cm* |
| No cocaine use        |                               |                     |                      |                            | 410 (100%)                        | 3108 ± 96           | 48.2 ± 0.5           | 33.9 ± 0.3                 |
| Cocaine               |                               |                     |                      |                            |                                   |                     |                      |                            |
| Consistently high     | 107 (44%)                     | 3033 ± 84           | 48.5 ± 0.5           | 33.5 ± 0.4                 |                                   |                     |                      |                            |
| Consistently moderate | 18 (7%)                       | 3064 ± 122          | 49.4 ± 0.8           | 32.5 ± 0.5                 |                                   |                     |                      |                            |
| Consistently low      | 22 (9%)                       | 2841 ± 108          | 49.0 ± 0.7           | 33.1 ± 0.5                 |                                   |                     |                      |                            |
| Increasing            | 15 (6%)                       | 2924 ± 118          | 48.4 ± 0.7           | 33.4 ± 0.5                 |                                   |                     |                      |                            |
| Decreasing            | 79 (33%)                      | 3038 ± 84           | 48.5 ± 0.5           | 33.5 ± 0.4                 |                                   |                     |                      |                            |
| Tobacco               |                               |                     |                      |                            |                                   |                     |                      |                            |
| No use                | 23 (9%)                       | 3168 ± 105          | 49.9 ± 0.7           | 33.7 ± 0.5                 | 269 (66%)                         | 3244 ± 101          | 48.7 ± 0.5           | 34.3 ± 0.3                 |
| Consistently high     | 50 (21%)                      | 2927 ± 85           | 48.0 ± 0.5           | 33.0 ± 0.4                 | 23 (6%)                           | 2980 ± 133          | 48.0 ± 0.7           | 33.6 ± 0.4                 |
| Consistently moderate | 35 (14%)                      | 3005 ± 93           | 48.6 ± 0.6           | 32.8 ± 0.4                 | 14 (3%)                           | 3069 ± 134          | 47.8 ± 0.7           | 33.5 ± 0.4                 |
| Consistently low      | 82 (34%)                      | 3026 ± 82           | 48.6 ± 0.5           | 33.4 ± 0.4                 | 68 (16%)                          | 3156 ± 110          | 48.3 ± 0.6           | 34.1 ± 0.3                 |
| Increasing            | 4 (2%)                        | 2753 ± 232          | 49.3 ± 1.5           | 32.8 ± 1.0                 | 0 (0%)                            |                     |                      |                            |
| Decreasing            | 47 (19%)                      | 3001 ± 88           | 47.9 ± 0.6           | 33.4 ± 0.4                 | 36 (9%)                           | 3090 ± 117          | 48.3 ± 0.6           | 33.9 ± 0.4                 |
| Alcohol               |                               |                     |                      |                            |                                   |                     |                      |                            |
| No use                | 59 (24%)                      | 2846 ± 93           | 49.2 ± 0.6           | 33.1 ± 0.4                 | 177 (43%)                         | 3121 ± 100          | 48.3 ± 0.5           | 33.9 ± 0.3                 |
| Consistently high     | 92 (38%)                      | 2874 ± 79           | 48.8 ± 0.5           | 32.9 ± 0.4                 | 26 (6%)                           | 2955 ± 116          | 47.8 ± 0.6           | 33.6 ± 0.4                 |
| Consistently moderate | 11 (4%)                       | 2985 ± 153          | 48.2 ± 1.0           | 33.5 ± 0.7                 | 8 (2%)                            | 3063 ± 172          | 47.7 ± 0.9           | 33.5 ± 0.5                 |
| Consistently low      | 11 (4%)                       | 2985 ± 150          | 47.8 ± 0.9           | 33.3 ± 0.7                 | 72 (17%)                          | 3141 ± 100          | 48.6 ± 0.5           | 34.0 ± 0.3                 |
| Increasing            | 4 (2%)                        | 3313 ± 243          | 49.3 ± 1.5           | 33.3 ± 1.1                 | 4 (1%)                            | 3165 ± 233          | 48.5 ± 1.2           | 34.1 ± 0.7                 |
| Decreasing            | 64 (26%)                      | 2876 ± 88           | 49.1 ± 0.6           | 32.9 ± 0.4                 | 123 (30%)                         | 3203 ± 93           | 48.5 ± 0.5           | 34.2 ± 0.3                 |
| Marijuana             |                               |                     |                      |                            |                                   |                     |                      |                            |
| No use                | 114 (47%)                     | 2906 ± 82           | 48.6 ± 0.5           | 32.9 ± 0.4                 | 332 (81%)                         | 3110 ± 77           | 49.4 ± 0.4           | 33.6 ± 0.2                 |
| Consistently high     | 25 (10%)                      | 2946 ± 111          | 48.5 ± 0.7           | 32.9 ± 0.5                 | 11 (3%)                           | 2963 ± 139          | 49.2 ± 0.7           | 33.4 ± 0.4                 |
| Consistently moderate | 18 (7%)                       | 2973 ± 116          | 48.7 ± 0.7           | 33.2 ± 0.5                 | 4 (1%)                            | 3284 ± 222          | 50.0 ± 1.2           | 34.7 ± 0.7                 |
| Consistently low      | 30 (12%)                      | 2980 ± 100          | 48.8 ± 0.6           | 33.1 ± 0.4                 | 19 (5%)                           | 3205 ± 123          | 49.5 ± 0.7           | 34.0 ± 0.4                 |
| Increasing            | 10 (4%)                       | 3004 ± 147          | 48.8 ± 0.9           | 33.4 ± 0.7                 | 2 (<1%)                           | 2973 ± 307          | 41.9 ± 1.6           | 34.1 ± 0.9                 |
| Decreasing            | 44 (18%)                      | 3072 ± 98           | 49.0 ± 0.6           | 33.6 ± 0.4                 | 42 (10%)                          | 3113 ± 98           | 49.6 ± 0.5           | 33.5 ± 0.3                 |

\* Mean ± SE.

infants born to the women who used no drugs was  $50.3 \pm 2.5$  cm, whereas that of the infants born to women who used any drugs was  $49.4 \pm 2.7$  cm ( $P < .05$ ).

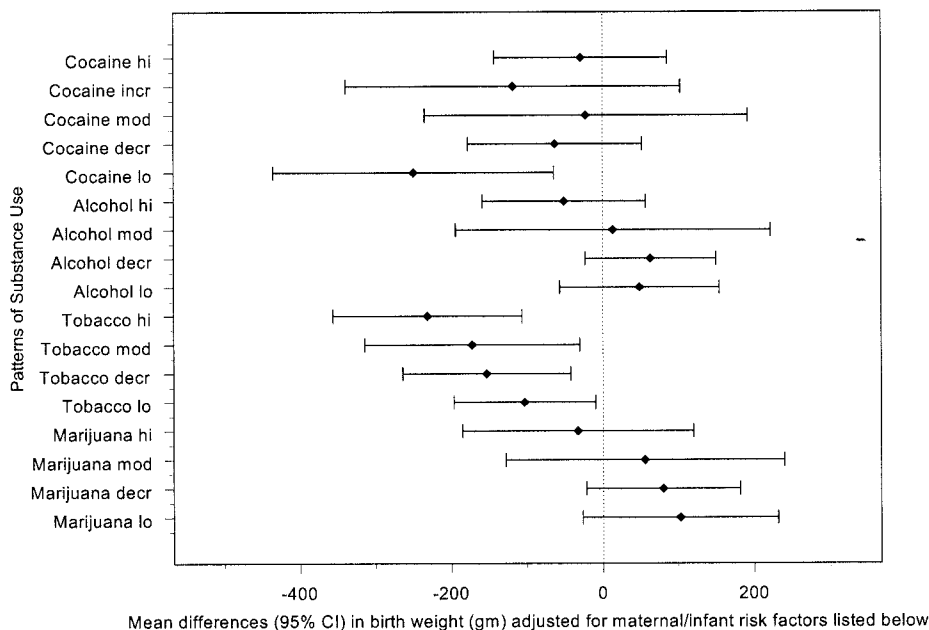
The relationships between patterns of substance use during pregnancy and neonatal birth weight, length, and head circumference in the cocaine-exposed and non-cocaine-exposed groups after adjustment for confounders can be seen in Table 4. The effects of patterns of opiate use are not shown because the numbers of cases involved was too small for meaningful interpretation. In the cocaine-exposed group, birth weight and head circumference were greatest for infants whose mothers had a pattern of decreasing use of cocaine, compared with other patterns of use. When effects of patterns of tobacco or alcohol use were examined among women who used cocaine, infant birth weight, length, and head circumference were greatest with no use or decreasing use of tobacco or alcohol. Similarly, among cocaine users who also used marijuana, growth parameters were greatest with decreasing marijuana use. Among women who did not use cocaine but used tobacco or alcohol, infant birth weight, length, and head circumference were greatest with no use, consistently low use, or decreasing use of these 2 drugs.

The effects of patterns of cocaine, alcohol, tobacco, and marijuana use during pregnancy on birth weight, length, and head circumference were each evaluated in multivariate analyses, with adjustment for clinical site, gestational age, infant gender, ma-

ternal race, socioeconomic status, prepregnancy weight, parity, maternal age, and patterns of use of the other 3 substances. In comparison with no cocaine use, a pattern of low cocaine use throughout both the early and late periods of pregnancy was associated with a significant decrease in the mean birth weight of almost 250 g (Fig 2), after adjustment for alcohol use, marijuana use, tobacco use, site, and maternal sociodemographic variables ( $P < .05$ ). Patterns of alcohol or marijuana use did not differentially affect birth weight. Patterns of consistently high, moderate, and low and decreasing tobacco use through early and late pregnancy, compared with no tobacco use, were associated with significant decreases in birth weight (deficits of 232, 173, 103, and 153 g, respectively), after adjustment for alcohol, marijuana, and cocaine use, site, and maternal sociodemographic variables.

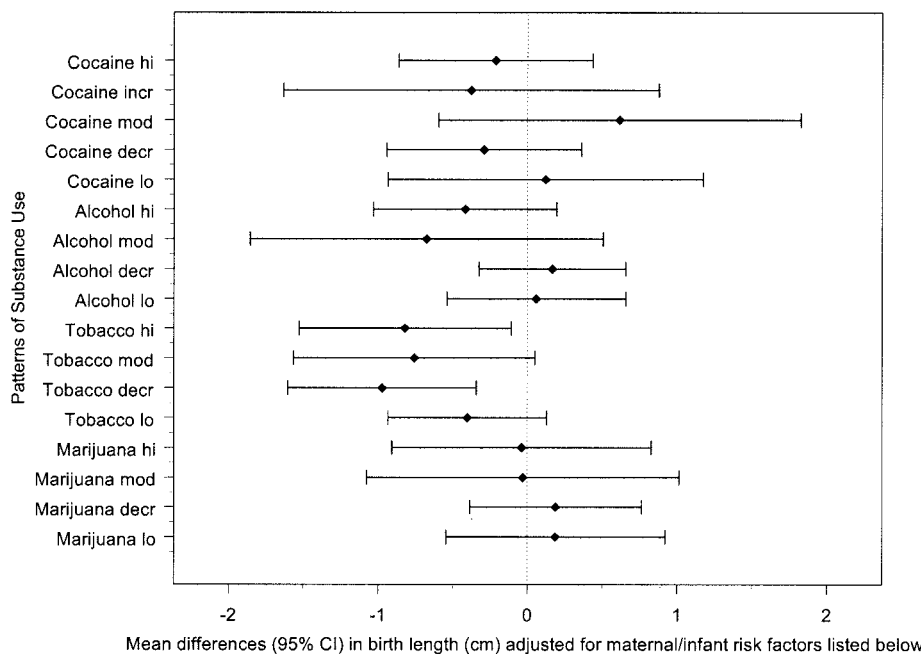
Within each drug use category, pairwise comparisons were used to examine the effects on birth weight of decreasing drug use between early (3 months before and during the first trimester) and late (second and third trimesters) pregnancy and consistently high, moderate, or low use throughout pregnancy. Low tobacco use was associated with an increase in birth weight of  $129 \pm 62$  g, compared with high use. Decreasing alcohol use was associated with an increase in birth weight of  $114 \pm 54$  g, compared with consistently high alcohol use ( $P < .05$ ).

The effects of patterns of drug use on infant birth length can be seen in Fig 3. Only patterns of tobacco use (high, moderate, and decreasing use patterns),



Note For each substance (cocaine, alcohol, tobacco, or marijuana), the numbers plotted are mean birth weight differences in gm (and associated 95% confidence intervals) between the particular pattern of use and no substance use. The mean differences and confidence intervals corresponding to a particular substance have been adjusted for clinical site, gestational age, gender, maternal race, SES (as measured by the Hollingshead index), pre-pregnancy weight, parity, age, as well as patterns of use for the other three substances, using multiple linear regression and multiple categorical coding (i.e., Consistently High (hi), Increasing (incr), Consistently Moderate (mod), Decreasing (decr), Consistently Low (lo), None). Increasing patterns for alcohol, tobacco, and marijuana have been dropped because of small numbers. A vertical bar placed at 0 gm indexes no difference.

Fig 2. Effects of patterns of cocaine, alcohol, tobacco, and marijuana use during pregnancy on infant birth weight.



Note For each substance (cocaine, alcohol, tobacco, or marijuana), the numbers plotted are mean birth length differences in cm (and associated 95% confidence intervals) between the particular pattern of use and no substance use. The mean differences and confidence intervals corresponding to a particular substance have been adjusted for clinical site, gestational age, gender, maternal race, SES (as measured by the Hollingshead index), pre-pregnancy weight, parity, age, as well as patterns of use for the other three substances, using multiple linear regression and multiple categorical coding (i.e., Consistently High (hi), Increasing (incr), Consistently Moderate (mod), Decreasing (decr), Consistently Low (lo), None). Increasing patterns for alcohol, tobacco, and marijuana have been dropped because of small numbers. A vertical bar placed at 0 cm indexes no difference.

Fig 3. Effects of patterns of cocaine, alcohol, tobacco, and marijuana use during pregnancy on infant birth length.

with adjustment for maternal clinical and demographic characteristics and cocaine, alcohol, and marijuana use, significantly affected birth length. High tobacco use was associated with a decrease of 0.82 cm and decreasing tobacco use was associated with a decrease of 0.98 cm, compared with no tobacco use ( $P < .05$  and  $P < .01$ , respectively).

The effects of patterns of drug use on head circumference are demonstrated in Fig 4. A consistently moderate pattern of cocaine use during the early and late periods, with adjustment for tobacco, alcohol, and marijuana use and clinical characteristics, demonstrated a decrease in head circumference of  $0.98 \pm 0.38$  cm, compared with no use ( $P < .05$ ). A consistently high pattern of tobacco use resulted in a decrease in head circumference of  $0.72 \pm 0.22$  cm ( $P < .01$ ) and a moderate pattern of use was associated with a decrease of  $0.89 \pm 0.25$  cm ( $P < .01$ ), compared with no tobacco use, with adjustment for cocaine, alcohol, and marijuana use and clinical characteristics. Patterns of prenatal alcohol or marijuana use did not affect infant head circumference, with adjustment for other drug use and clinical characteristics.

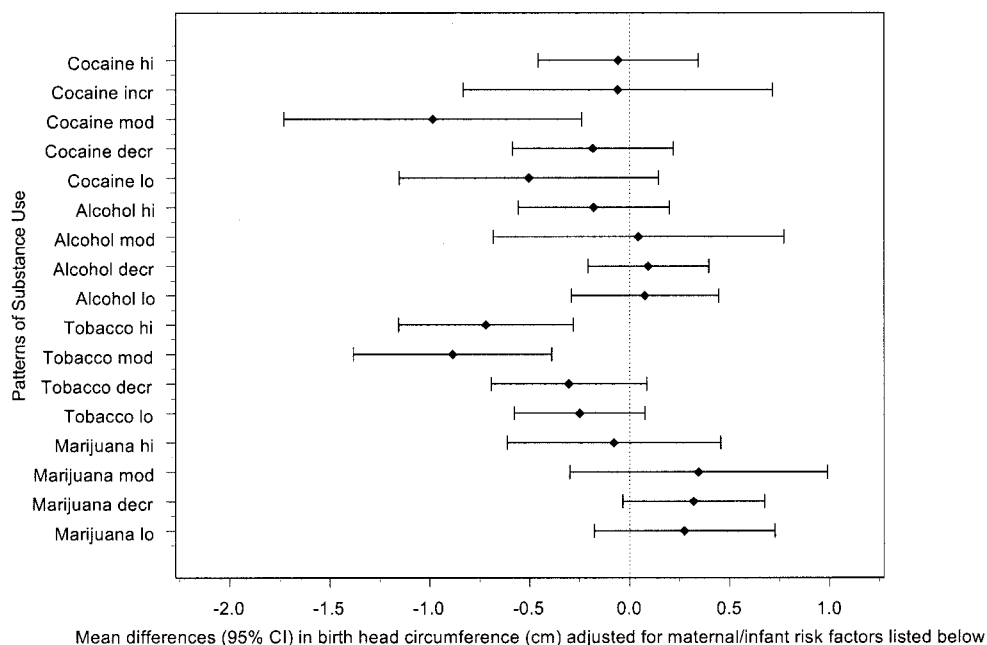
Within each drug category, when decreasing use of cocaine, alcohol, tobacco, or marijuana during pregnancy was compared with other patterns of use, using pairwise comparisons, decreasing use of cocaine resulted in an increase in head circumference of  $0.80 \pm 0.34$  cm, compared with moderate cocaine use ( $P < .05$ ). Low tobacco use, compared with both high and moderate tobacco use, had positive effects on

head circumference (low versus moderate tobacco use was associated with an increase in head circumference of  $0.64 \pm 0.25$  cm,  $P < .05$ ; low versus high tobacco use was associated with an increase in head circumference of  $0.47 \pm 0.22$  cm ( $P < .05$ ).

## DISCUSSION

We have reported on the association between patterns of drug use and effects on growth parameters at birth, for term pregnancies, in a large sample of cocaine-exposed and non-cocaine-exposed women who delivered their infants in urban hospital settings. This study is unique, in that the effects of patterns of multidrug use during pregnancy were analyzed, rather than use in a single trimester or drug use averaged throughout the pregnancy. This is also the first report to examine substance use and compare the effects of patterns of use of different drugs (high, moderate, low, increasing, or decreasing use throughout pregnancy) on growth parameters at term gestation, with adjustment for site, prepregnancy weight, multidrug use, and socioeconomic status.

Multidrug use was common among users of cocaine, as well as in the comparison group in this study. Among cocaine users, 75% admitted to alcohol use, 90% to tobacco use, and 53% to marijuana use. Among women who did not use cocaine, 57% admitted to alcohol use, 34% to tobacco use, and 19% to marijuana use. The frequency of multidrug use among both cocaine-exposed and non-cocaine-ex-



**Note** For each substance (cocaine, alcohol, tobacco, or marijuana), the numbers plotted are mean birth head circumference differences in cm (and associated 95% confidence intervals) between the particular pattern of use and no substance use. The mean differences and confidence intervals corresponding to a particular substance have been adjusted for clinical site, gestational age, gender, maternal race, SES (as measured by the Hollingshead index), pre-pregnancy weight, parity, age, as well as patterns of use for the other three substances, using multiple linear regression and multiple categorical coding (i.e., Consistently High (hi), Increasing (incr), Consistently Moderate (mod), Decreasing (decr), Consistently Low (lo), None). Increasing patterns for alcohol, tobacco, and marijuana have been dropped because of small numbers. A vertical bar placed at 0 cm indexes no difference.

**Fig 4.** Effects of patterns of cocaine, alcohol, tobacco, and marijuana use during pregnancy on infant head circumference.

posed women in this study was higher than that in recent reports.<sup>1,2,8</sup> The present study screened all women for eligibility and did not oversample or exclude women with heavy cocaine or alcohol use, as in previous reports.<sup>1,7,20–22</sup>

A limitation of this study was that the history of use of cocaine, alcohol, tobacco, and marijuana during the periconceptional period and each trimester of pregnancy was obtained at 1 month after delivery of the infant. This method of ascertainment of drug use has the drawbacks inherent in any assessment of use by recall and may result in understatement of alcohol use. Postnatal self-report measures of maternal cocaine use, however, have been found to be as effective as prenatal measures in predicting neurobehavioral outcomes.<sup>23</sup> The 150 women who were not part of the analysis sample could have introduced bias. There were no interview data available to evaluate patterns of drug use among the women who were not biological mothers ( $n = 56$ ) or those who denied use but exhibited evidence of drug use in the infants' meconium analyses ( $n = 94$ ). As expected, cocaine exposure was higher in the group not included in the analysis sample, compared with those in the sample. Older maternal age and lower prepregnancy weight for the excluded women can be attributed to the cocaine exposure.

Another limitation was that we are unable to provide insight into the mechanism of growth restriction among term infants in this study. Other investigators suggested that maternal and obstetric risk factors,

lack of prenatal care, undernutrition, and effects of cocaine and nicotine on uterine blood flow might be involved in the mechanism of growth restriction.<sup>22,24–29</sup> Recently, an interaction between metabolic genes and cigarette smoking was demonstrated.<sup>12</sup>

In this study, infant birth weight, length, and head circumference were lower in the presence of multi-drug use. Women who used alcohol, tobacco, and cocaine had neonates with lower birth growth parameters, compared with infants of women who did not use these substances. When effects of substance use on birth weight, length, and head circumference were evaluated in multivariate analyses, tobacco use had the greatest effect on all 3 parameters. The effects of tobacco use on birth weight, length, and head circumference seemed to be dose-dependent.

Jacobson et al<sup>7</sup> recruited moderate-to-heavy users of alcohol or cocaine and a random sample of lower-level drinkers and abstainers ( $n = 417$ ) and found that birth weight was related only to alcohol use and smoking, length only to alcohol use, and head circumference only to opiate use. Eyler et al<sup>2</sup> evaluated 154 cocaine users and 154 matched nonusers and found no difference in birth weight or length between infants born to cocaine users and control infants, after controlling for the effects of marijuana, alcohol, and tobacco use. Infant head and chest circumferences were smaller for infants of cocaine users who also smoked tobacco. When effects of substance use in each trimester were evaluated, there was a

negative correlation between cocaine use in the third trimester and infant length and head circumference at birth. A disproportionate adverse effect on head growth at birth, compared with overall growth or birth weight, was noted by some investigators<sup>20</sup> but not others.<sup>30,31</sup>

The majority of studies that evaluated the effects of drug use on fetal growth compared the outcomes for exposed and unexposed infants without evaluating the confounding effects of prematurity or timing of use during pregnancy.<sup>16,21</sup> We focused our study only on women with term gestation, because cocaine and tobacco use are associated with preterm delivery. The questionnaire used in this study to obtain the history of substance use during pregnancy was very detailed; it allowed the interviewer to record the use of individual drugs in each trimester, as well as the level of use of each drug, permitting patterns of use to be categorized. Among cocaine-using women, the 2 most frequent patterns of use were consistently high use throughout pregnancy (44%) and decreasing use (33%). Women in the cocaine-exposed group who used alcohol also tended to be consistently high users of alcohol (38%) or decreasing users (26%); those who used tobacco tended to have a pattern of low use of tobacco (34%) throughout pregnancy, and those who used marijuana tended to be decreasing users (18%). The frequency of alcohol, tobacco, and marijuana use was higher among non-cocaine-exposed women in this study than reported in the literature; however, when patterns of use were evaluated, the majority of women reported either low or decreasing use of these substances.

When the effects of drug use on birth weight were compared in this study, low cocaine use throughout pregnancy was associated with a negative effect on birth weight (−250 g) that was similar to that of high tobacco use (−232 g). Cocaine thus seems to be more potent than tobacco, and tobacco use in the context of cocaine use may have different implications than tobacco use alone.

Fetal growth accelerates in the third trimester, and drug use in pregnancy affects the growth of term infants more than that of preterm infants.<sup>32</sup> We found that decreasing or low tobacco use was the only pattern associated with greater birth weight, length, and head circumference, compared with decreasing patterns of use of other drugs. The clinical implications of this study are that illicit drug use as well as alcohol and tobacco use should be curtailed during pregnancy. Patterns of smoking cessation or reduction are associated with increased birth weight in term gestation.<sup>10,11</sup> Public health programs must emphasize the importance of reduction or cessation of the use of all substances during pregnancy, including cocaine, tobacco, alcohol, and marijuana.

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