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COCAINE AND TOBACCO USE AND THE RISK OF SPONTANEOUS ABORTION

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ABSTRACT

Background Cigarette smoking and cocaine use may be risk factors for spontaneous abortion, but data supporting such a link are limited.

Methods We studied the associations between cocaine and tobacco use and spontaneous abortion among pregnant adolescents and women (age range, 14 to 40 years) who sought care at an inner-city emergency department. A total of 400 adolescents and women had spontaneous abortions either at study entry or during follow-up (which lasted until 22 weeks' gestation), and 570 adolescents and women remained pregnant past 22 weeks' gestation. Cocaine use was measured at base line by self-reports and analysis of urine and hair samples. Cigarette smoking was measured by self-reports and urine analysis.

Results The adolescents and women in both groups were predominantly black and of lower socioeconomic status. Among those who had spontaneous abortions, 28.9 percent used cocaine on the basis of hair analysis and 34.6 percent smoked on the basis of a urine cotinine assay, as compared with 20.5 percent and 21.8 percent, respectively, of the adolescents and women who did not have spontaneous abortions. The presence of cocaine in hair samples was independently associated with an increase in the occurrence of spontaneous abortion (odds ratio, 1.4; 95 percent confidence interval, 1.0 to 2.1) after adjustment for demographic and drug-use variables. However, the use of cocaine as measured by self-reports and by urine analysis was not. The presence of cotinine in urine was also independently associated with an increased risk of spontaneous abortion (odds ratio, 1.8; 95 percent confidence interval, 1.3 to 2.6). Twenty-four percent of the risk of spontaneous abortion could be related to cocaine or tobacco use.

Conclusions Cocaine use and tobacco use were common in our study population and were associated with a significant risk of spontaneous abortion. (N Engl J Med 1999;340:333-9.)

SPONTANEOUS abortion is the most common adverse outcome of pregnancy.[1] Heralded by vaginal bleeding, it is associated with considerable pain, suffering, and medical costs. Little is known about the influences of lifestyle on spontaneous abortion, although the use of illicit drugs has been implicated as a factor.[2-4]

Cocaine use early in pregnancy decreases uterine and placental blood flow by inhibiting the reuptake of norepinephrine, which causes arterial vasoconstriction.[5,6] In rats, exposure to cocaine increases the frequency of reabsorption of fetuses, the equivalent of spontaneous abortion in humans.[7] Nicotine, the main addictive compound of tobacco smoke, is also a strong vasoconstrictor that reduces uterine and placental blood flow.[8] Other toxic components of tobacco smoke include carbon monoxide, which binds to hemoglobin and decreases the availability of oxygen to the fetus, and cyanide, which depletes vitamin B_{12}, a necessary cofactor for fetal growth and development.

In most, but not all, previous studies of cocaine use during pregnancy and spontaneous abortion, the women's current use of cocaine, as assessed by self-reports or urine analysis, was related to their history of spontaneous abortion.[2-4,9] One small, prospective study did not find a significant link between cocaine use and incident spontaneous abortion.[10] Cigarette smoking, as measured by self-reports, has been associated with spontaneous abortion in some but not all previous studies.[11-14]

We designed a case–control study to compare

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drug use during pregnancy among inner-city adolescents and women who had spontaneous abortions and adolescents and women who remained pregnant after 22 weeks' gestation.

METHODS

Study Subjects

Adolescent girls and women from 14 to 40 years of age who presented to the emergency department of the Hospital of the University of Pennsylvania between August 1995 and July 1997 and who resided in 1 of 12 areas defined by ZIP Code in inner-city Philadelphia were screened for pregnancy. Adolescents and women who had not had a hysterectomy were asked standardized questions about the date and quality of their last menstrual period. All those who reported that their last normal menstrual period had occurred more than 22 weeks earlier or less than 28 days earlier were not studied further.[15] All others underwent urine pregnancy tests, and those with a positive test were further screened for eligibility. Fifteen percent of these adolescents and women were deemed ineligible for the following reasons: documented ectopic, molar, or twin pregnancy; limited ability to speak English; acute mental illness; birth of a child or therapeutic abortion within 14 days before the emergency department visit; or complete spontaneous abortions within 4 to 14 days before the emergency department visit (during which time the pregnancy test would remain positive but an incident spontaneous abortion could not be classified unequivocally).

Among the 1347 pregnant adolescents and women who were eligible for the study, 71 (5 percent) declined to participate, 10 (1 percent) did not complete the study questionnaire, and 1266 (94 percent) gave written informed consent for the initial interview, follow-up telephone interviews at 16 and 22 weeks' gestation, medical-record review, and collection of urine, blood, and hair samples. The protocol and consent procedures were approved by the institutional review board of the University of Pennsylvania.

The adolescents and women were divided into two groups: those who had spontaneous abortions and those who carried their pregnancies past 22 weeks' gestation (Fig. 1). As shown in Figure 1, a further 249 women (20 percent) were excluded on the basis of events that occurred during follow-up, and 47 women (4 percent) were lost to follow-up. The status of the 970 adolescents and women included in the study was determined by means of follow-up interview (96.4 percent) or analysis of medical records (3.6 percent). The chief reasons for visiting the emergency department were vaginal bleeding or possible complications of pregnancy in the case of 557 participants (57.4 percent), abdominal or pelvic pain in 184 (19.0 percent), nausea or vomiting in 192 (19.8 percent), and other reasons in 37 (3.8 percent).

Spontaneous Abortion

The spontaneous-abortion group included anyone who had a spontaneous abortion before 22 weeks' gestation. Among the 400 adolescents and women in this group, 211 had spontaneous abortions within the three days before or the two days after the emergency department visit (the base-line period). These included inevitable abortions, incomplete abortions, missed abortions, and complete abortions (according to standardized definitions) identified on the basis of gynecologic examinations, pelvic ultrasonography, and serial measurements of the beta subunit of human chorionic gonadotropin in serum.[16] The other 189 adolescents and women reported having a spontaneous abortion during the follow-up period — that is, more than 2 days after enrollment and by 22 weeks' gestation.

The medical or pathology records of 61.3 percent of the adolescents and women in the spontaneous-abortion group were reviewed. When the analysis included only cases of spontaneous abortion confirmed in this way, the results were almost identical to those for the group as a whole.

Gestational Age

Gestational age was calculated on the basis of the date of last normal menstrual period and was verified by ultrasonography during the first or second trimester in 279 of the adolescents and

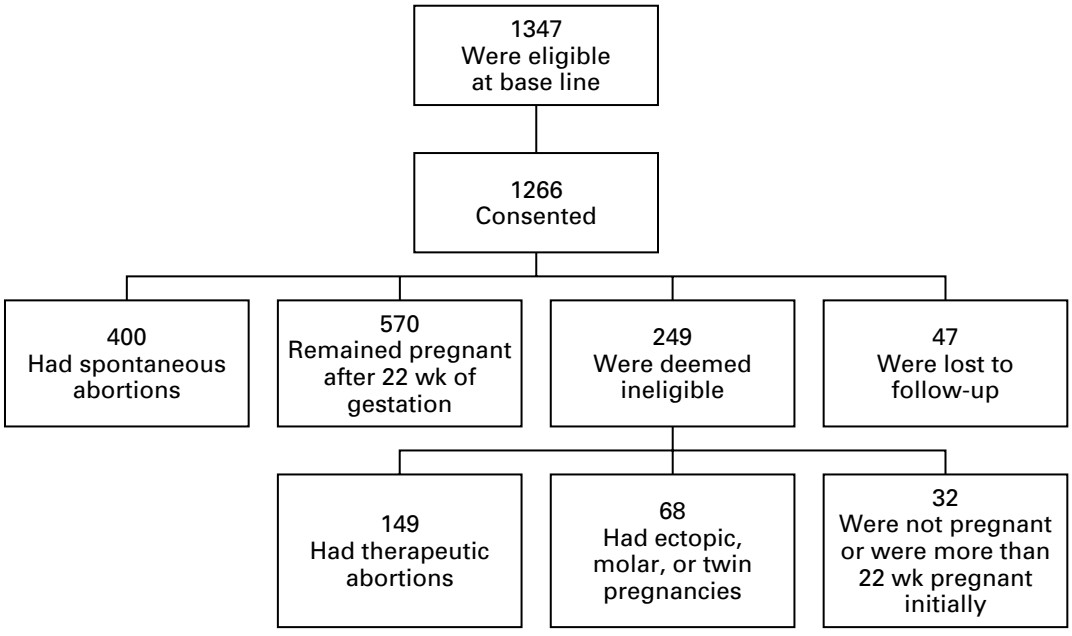

Figure 1. Number of Adolescents and Women Enrolled in the Study and Reasons for Exclusion.

women (28.8 percent). For 200 of these 279 adolescents and women (71.7 percent), the dates calculated with this method were within three weeks of the dates calculated by measuring crown–rump length. The gestational age at the time of spontaneous abortion was known for three quarters of the subjects in this group. For these adolescents and women, spontaneous abortion was categorized according to whether it occurred before 10 weeks' gestation or at 10 weeks or later.

Measures of Exposure to Cocaine, Marijuana, Cigarettes, and Alcohol

In a standardized, 45-minute interview conducted by one of four trained interviewers at base line, the adolescents and women were asked about recent use of cocaine, "crack" cocaine, marijuana, cigarettes, and alcohol and the frequency and quantity of each substance used during the month after the last menstrual period and the three months before the last menstrual period. Blood, urine, and hair samples were collected at this time.

All biochemical tests were performed in batches, with positive and negative controls, and with specimens from both groups of subjects randomly mixed by technicians unaware of the subjects' questionnaire results. Urine samples were assayed for the major metabolites of cocaine (benzoylecgonine), marijuana (cannabinoids), amphetamines, and opiates by automated fluorescence polarization immunoassay (Abbott Laboratories, Abbott Park, Ill.). The presence of cotinine, the chief metabolite of nicotine, in the urine was assessed by a microplate enzyme-linked immunosorbent assay (STC Diagnostics, Bethlehem, Pa.). All urine samples containing any of these substances were reanalyzed by gas chromatography–mass spectrometry. The results of assays were considered positive if they exceeded the following threshold concentrations: 300 ng of benzoylecgonine per milliliter, indicating cocaine use; 50 ng of cannabinoids per milliliter, indicating marijuana use; 300 ng of *d*-amphetamine per milliliter, indicating amphetamine use; 200 ng of morphine per milliliter, indicating opiate use; 500 ng of cotinine per milliliter, indicating active cigarette smoking.

Cocaine was also measured in hair specimens by Psychemedics (Culver City, Calif.) with a radioimmunoassay.[17,18] Since hair grows at a rate of approximately 13 mm per month,[19] assay of a 3.9-cm length of hair at entry covered the early gestational period for all adolescents and women who were enrolled before 12 weeks' gestation. Results were considered positive above a threshold of 1.2 ng of cocaine per milligram. Positive results were also divided into three groups: ≤9.7 ng of cocaine per milligram, 9.8 to 39.0 ng of cocaine per milligram, and ≥39.1 ng of cocaine per milligram. Before the assay, all specimens were washed for 15 minutes with dry ethanol, then three times with phosphate buffer for 30 minutes each, then two times in phosphate buffer for 1 hour each in a water bath with shaking at 120 cycles per minute. The medium was then analyzed for cocaine. The results for hair specimens that had been externally contaminated with cocaine, as evidenced by the presence of cocaine in the washing medium, were categorized as negative because the cocaine detected may not have represented internal use.[18,20] Among nine specimens analyzed on two separate occasions, the reliability between results was 0.98. The results of cocaine measurements in hair were available for 92.4 percent of the subjects, and the results of cocaine measurements in urine were available for 96.5 percent.

Statistical Analysis

The differences between groups were analyzed with Student's t-test for continuous variables and the chi-square test for categorical variables. The odds ratios associated with cigarette smoking, cocaine use, and the use of other drugs of abuse were calculated by comparing the control group with the entire group of adolescents and women who had spontaneous abortions, the subgroup that had spontaneous abortions during the base-line period, and the subgroup that had spontaneous abortions during follow-up.

All variables identified on the basis of biologic plausibility and preliminary analyses as possible confounders were included in logistic-regression models, which were then simplified with use of a backward-elimination technique. All final models included the same set of statistically significant covariates, and each final model also included one of the measures of cocaine use (hair analysis, urine analysis, or self-reports), tobacco use (urine analysis or self-reports), alcohol use (self-reports), and use of marijuana (urine analysis). The interaction between the variables of cocaine in the hair and urinary cotinine and the other covariates in the final model were not significant. Attributable risk was calculated from these multivariate adjusted odds ratios according to the method of Bruzzi et al.[21]

RESULTS

Most of the adolescents and women who were enrolled in this study were black, were receiving public assistance, and had no more than a high-school education (Table 1). The mean duration of gestation at enrollment was about 10 weeks, and approximately three quarters of the adolescents and women were 12 weeks pregnant or less. Those who had spontaneous abortions were less likely to have sought prenatal care and to be living with the father of the child than those who did not have spontaneous abortions.

Among the adolescents and women who had spontaneous abortions, 28.9 percent (27.1 percent of the subgroup with a spontaneous abortion at base line and 30.9 percent of the subgroup with a spontaneous abortion during follow-up) had used cocaine on the basis of hair analysis, as compared with 20.5 percent of the adolescents and women who did not have spontaneous abortions (odds ratio, 1.6; 95 percent confidence interval, 1.2 to 2.1) (Table 2). The results of hair analysis were more than four times as likely to be positive as self-reports of cocaine use, and the results of urine analysis were 1.5 times as likely to be positive. The results of urine analysis were more likely to be positive among the adolescents and women who had spontaneous abortions than among those whose did not have spontaneous abortions (odds ratio, 1.4; 95 percent confidence interval, 0.9 to 2.3), whereas the rates of self-reported use since the last menstrual period were similar between the two groups (odds ratio, 1.2; 95 percent confidence interval, 0.7 to 2.3) (Table 2).

Cotinine was detected in the urine of 34.6 percent of the adolescents and women who had spontaneous abortions and 21.8 percent of those who did not have spontaneous abortions. The presence of cotinine in urine was significantly associated with spontaneous abortion (odds ratio, 1.9; 95 percent confidence interval, 1.4 to 2.6). Self-reported smoking during pregnancy was also associated with a marginally significant increase in spontaneous abortion (odds ratio, 1.4; 95 percent confidence interval, 1.0 to 1.9), as was self-reported alcohol use either before or after the last menstrual period (Table 2). Marijuana use, as assessed by self-reports or urinary testing, was not significantly different between the two groups.

In multivariate analyses that included other variables, the odds of a spontaneous abortion were 1.4 (95

TABLE 1. CHARACTERISTICS OF THE ADOLESCENTS AND WOMEN WHO HAD SPONTANEOUS ABORTIONS AND OF THOSE WHO DID NOT.*

CHARACTERISTIC	NO SPONTANEOUS ABORTION (N=570)	SPONTANEOUS ABORTION (N=400)	SPONTANEOUS ABORTION AT BASE LINE (N=211)	SPONTANEOUS ABORTION DURING FOLLOW-UP (N=189)
Age — yr	23±5	23±6	24±6	23±5
Duration of gestation — wk	10.7±3.9	9.8±3.3†	10.3±3.5	9.3±3.0†
Receiving public assistance — no. (%)	312 (54.9)	224 (56.0)	114 (54.0)	110 (58.2)
Living with father of child — no. (%)	251 (44.2)	151 (37.8)‡	77 (36.5)‡	74 (39.2)
Race — no. (%)				
Black	517 (90.9)	365 (91.2)	194 (91.9)	171 (90.5)
White	18 (3.2)	15 (3.8)	8 (3.8)	7 (3.7)
Other	34 (6.0)	20 (5.0)	9 (4.3)	11 (5.8)
Years of education — no. (%)				
<12 yr	213 (37.4)	152 (38.0)	79 (37.4)	73 (38.6)
12 yr	252 (44.3)	171 (42.8)	88 (41.7)	83 (43.9)
>12 yr	104 (18.3)	77 (19.2)	44 (20.9)	33 (17.5)
No. of prior spontaneous abortions	0.5±0.8	0.5±0.9	0.5±0.9	0.5±0.9
Gravidity	2.2±2.0	2.4±2.0	2.4±2.1	2.4±1.9
Parity	1.2±1.5	1.2±1.4	1.2±1.4	1.3±1.4
Body-mass index§	26.0±7.0	26.6±6.6	26.9±6.8	26.2±6.3
History of gonorrhea — no. (%)	123 (21.6)	85 (21.2)	39 (18.6)	46 (24.3)
History of syphilis — no. (%)	30 (5.3)	24 (6.0)	12 (5.7)	12 (6.3)
HIV-positive — no. (%)¶	4 (0.7)	2 (0.5)	1 (0.5)	1 (0.5)
Prenatal care — no. (%)				
No; did not know she was pregnant	140 (24.6)	100 (25.1)	48 (22.7)	52 (27.7)
No	189 (33.2)	198 (49.6)‖	108 (51.2)**	90 (47.9)
Yes	240 (42.2)	101 (25.3)††	55 (26.1)	46 (24.5)††

*Data on public assistance were missing for two subjects in the group that did not have a spontaneous abortion; data on living with father of child were missing for two subjects in the group that did not have a spontaneous abortion; data on race were missing for one subject in the group that did not have a spontaneous abortion; data on years of education were missing for one subject in the group that did not have a spontaneous abortion; data on history of gonorrhea were missing for one subject in the group that did not have a spontaneous abortion and one subject in the group that had an abortion during the base-line period; data on history of syphilis were missing for one subject in the group that did not have a spontaneous abortion; and data on prenatal care were missing for one subject in the group that did not have a spontaneous abortion and one subject who had a spontaneous abortion during follow-up. Plus–minus values are means ±SD. Because of rounding, percentages may not total 100.

†P<0.001 for the comparison with the group that did not have a spontaneous abortion.

‡P=0.05 for the comparison with the group that did not have a spontaneous abortion.

§The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

¶HIV denotes human immunodeficiency virus.

‖P=0.02 for the comparison with the group that did not have a spontaneous abortion.

**P=0.01 for the comparison with the group that did not have a spontaneous abortion.

††P=0.003 for the comparison with the group that did not have a spontaneous abortion.

percent confidence interval, 1.0 to 2.1) for adolescents and women in whom cocaine was detected in hair (Table 3). The odds ratios were similar whether the spontaneous abortions occurred at base line or during follow-up. The presence of cotinine in urine was independently and significantly related to an increased risk of spontaneous abortion (odds ratio, 1.8; 95 percent confidence interval, 1.3 to 2.6), a finding that was somewhat stronger among the adolescents and women who had spontaneous abortions during follow-up. There was no significant interaction between any measure of cocaine use and urinary cotinine on the basis of either stratified or multivariate analyses. Neither self-reported cigarette smoking nor self-reported cocaine use was significantly related to a risk of spontaneous abortion after adjustment for confounders. Marijuana and alcohol use were also not independently related to a risk of spontaneous abortion. There was no dose–response relation between the amount of cocaine in hair and the risk of spontaneous abortion. The respective odds ratios associated with low, medium, and high levels of cocaine in hair, as compared with no detectable levels, were 1.5 (95 percent confidence interval, 1.0 to 2.4), 1.1 (95 percent confidence interval, 0.7 to 1.7), and 1.6 (95 percent confidence interval, 1.0 to 2.5).

The high prevalence of cocaine and tobacco use suggests that a substantial proportion of spontaneous

TABLE 2. SELF-REPORTED AND LABORATORY MEASUREMENTS OF SUBSTANCE USE AMONG ADOLESCENTS AND WOMEN WHO HAD SPONTANEOUS ABORTIONS AND AMONG THOSE WHO DID NOT.

VARIABLE	NO SPONTANEOUS ABORTION (N=570)	SPONTANEOUS ABORTION (N=400)		SPONTANEOUS ABORTION AT BASE LINE (N=211)		SPONTANEOUS ABORTION DURING FOLLOW-UP (N=189)	
	NO. (%)	NO. (%)	OR (95% CI)*	NO. (%)	OR (95% CI)*	NO. (%)	OR (95% CI)*
Self-reports							
Cocaine use (including crack cocaine)							
Never	511 (89.6)	345 (86.2)	1.0†	186 (88.2)	1.0†	159 (84.1)	1.0†
Before last menstrual period	36 (6.3)	36 (9.0)	1.5 (0.9–2.4)	15 (7.1)	1.1 (0.6–2.1)	21 (11.1)	1.9 (1.1–3.3)
Since last menstrual period	23 (4.0)	19 (4.8)	1.2 (0.7–2.3)	10 (4.7)	1.2 (0.6–2.6)	9 (4.8)	1.3 (0.6–2.8)
Tobacco use‡							
Never	333 (58.4)	216 (54.3)	1.0†	121 (57.6)	1.0†	95 (50.5)	1.0†
In the past	107 (18.8)	63 (15.8)	0.9 (0.6–1.3)	27 (12.9)	0.7 (0.4–1.1)	36 (19.1)	1.2 (0.8–1.8)
Currently	130 (22.8)	119 (29.9)	1.4 (1.0–1.9)	62 (29.5)	1.3 (0.9–1.9)	57 (30.3)	1.5 (1.0–2.2)
Marijuana use							
Never	233 (40.9)	155 (38.8)	1.0†	89 (42.2)	1.0†	66 (34.9)	1.0†
Before last menstrual period	241 (42.3)	166 (41.5)	1.03 (0.8–1.4)	76 (36.0)	0.8 (0.5–1.1)	90 (47.6)	1.4 (0.9–2.0)
Since last menstrual period	96 (16.8)	79 (19.8)	1.2 (0.8–1.6)	46 (21.8)	1.2 (0.8–1.7)	33 (17.5)	1.2 (0.8–1.8)
Alcohol use							
Never	278 (48.8)	166 (41.5)	1.0†	82 (38.9)	1.0†	84 (44.4)	1.0†
Before last menstrual period	126 (22.1)	102 (25.5)	1.4 (1.0–1.9)	60 (28.4)	1.6 (1.1–2.4)	42 (22.2)	1.1 (0.7–1.7)
Since last menstrual period	166 (29.1)	132 (33.0)	1.3 (1.0–1.8)	69 (32.7)	1.4 (0.97–2.0)	63 (33.3)	1.3 (1.0–1.8)
Laboratory measurements§							
Cocaine detected in hair	107 (20.5)	108 (28.9)	1.6 (1.2–2.1)	54 (27.1)	1.4 (1.0–2.1)	54 (30.9)	1.7 (1.2–2.5)
Cocaine detected in urine	35 (6.4)	34 (8.8)	1.4 (0.9–2.3)	17 (8.5)	1.4 (0.7–2.5)	17 (9.1)	1.5 (0.8–2.7)
Cotinine detected in urine	110 (21.8)	118 (34.6)	1.9 (1.4–2.6)	55 (30.2)	1.6 (1.1–2.3)	63 (39.6)	2.4 (1.6–3.4)
Cannabinoids detected in urine	118 (21.5)	98 (25.3)	1.2 (0.9–1.7)	49 (24.4)	1.2 (0.8–1.7)	49 (26.3)	1.3 (0.9–1.9)
Opiates detected in urine	11 (2.1)	11 (2.9)	1.4 (0.6–3.3)	7 (3.6)	1.8 (0.7–4.6)	4 (2.2)	1.1 (0.3–3.4)
Amphetamines detected in urine	4 (0.7)	5 (1.3)	1.8 (0.5–6.7)	1 (0.5)	0.7 (0.1–6.1)	4 (2.2)	3.0 (0.7–12.1)

*OR denotes unadjusted odds ratio, and CI confidence interval.

†This group is the reference group.

‡Data on tobacco use were missing for two subjects in the spontaneous-abortion group (one in each subgroup).

§Data on hair analysis for cocaine were available for 522 subjects in the group that did not have a spontaneous abortion and 374 subjects in the spontaneous-abortion group (199 in the subgroup with abortion at base line and 175 in the subgroup with abortion during follow-up); data on urine analysis for cocaine were available for 549 and 387 (201 and 186) subjects, respectively; data on urine analysis for cotinine were available for 504 and 341 (182 and 159) subjects, respectively; data on urine analysis for cannabinoids were available for 548 and 387 (201 and 186) subjects, respectively; data on urine analysis for opiates were available for 535 and 377 (196 and 181) subjects, respectively; and data on urine analysis for amphetamines were available for 549 and 387 (201 and 186) subjects, respectively.

abortions are attributable to exposure to these two substances. Indeed, given our risk estimates, cocaine use (8 percent) and smoking (16 percent) together would account for 24 percent of the spontaneous abortions among these inner-city adolescents and women.

DISCUSSION

Our results suggest that cigarette smoking and cocaine use are independently associated with an increased risk of spontaneous abortion. The absence of a dose–response relation suggests that any level of exposure to cocaine, rather than a high level of exposure, is associated with spontaneous abortion, but the relatively small number of adolescents and women with high levels of exposure and, perhaps, variations in the timing of cocaine use and in the incorporation of the drug into hair could make a dose–response effect difficult to detect.

Our study has several strengths. First, by enrolling adolescents and women early in pregnancy who were seen at an emergency department rather than in a prenatal care setting, we recruited those at high risk for cocaine use. Second, we used sensitive biologic measures of drug use. Third, the similarity of results between the adolescents and women who had spontaneous abortions during the base-line period and those who had spontaneous abortions during follow-up reduces the possibility of selection bias. Finally, the rates of recruitment, retention, and acquisition of complete data were high, adding support to the validity of the results. The study also had some limitations. The size of the effects of cocaine and tobacco use was moderate. Unmeasured factors such as the extent of care seeking, other health-related behavior, dietary factors, levels of health consciousness, and asymptomatic genital infection, if they are related to cocaine use and to spontaneous abortion, may have confounded the study results.

The results of studies that examined the association between current cocaine use and spontaneous abortion on the basis of patients' histories and obstetrical

TABLE 3. MULTIVARIATE ANALYSIS OF RISK FACTORS FOR SPONTANEOUS ABORTION AMONG INNER-CITY ADOLESCENTS AND WOMEN.*

VARIABLE	SPONTANEOUS ABORTION		SPONTANEOUS ABORTION AT BASE LINE		SPONTANEOUS ABORTION DURING FOLLOW-UP	
	ODDS RATIO	95% CI	ODDS RATIO	95% CI	ODDS RATIO	95% CI
Cocaine detected in hair	1.4	1.0–2.1	1.4	0.9–2.2	1.5	0.9–2.3
Cotinine detected in urine	1.8	1.3–2.6	1.6	1.0–2.4	2.2	1.4–3.5
Cannabinoids detected in urine	0.9	0.6–1.3	0.8	0.5–1.3	1.0	0.6–1.6
Self-reported alcohol use	0.9	0.7–1.3	0.9	0.6–1.4	0.9	0.6–1.3
Living with father of child	0.8	0.6–1.1	0.7	0.5–1.1	0.8	0.6–1.2
Week of gestation at interview (per wk)	0.9	0.9–1.0	1.0	0.9–1.0	0.9	0.8–0.9
Prenatal care†						
No	1.7	1.2–2.5	1.9	1.2–2.9	1.6	1.0–2.6
Yes	0.8	0.5–1.3	0.8	0.5–1.4	0.8	0.5–1.4

*All variables shown were included in the final model. The initial model included age, duration of gestation, body-mass index, number of prior spontaneous abortions, gravidity, parity, race (black, white, or other), prenatal care (no, because subject did not know she was pregnant; yes; or no), level of education (<12 years, 12 years, or >12 years), history of gonorrhea (yes or no), history of syphilis (yes or no), HIV status (positive or negative), receiving public assistance (yes or no), living with father of child (yes or no), alcohol use since last menstrual period (yes or no), cocaine detected in hair (yes or no), cotinine detected in urine (yes or no), cannabinoids detected in urine (yes or no), amphetamines detected in urine (yes or no), and opiates detected in urine (yes or no). CI denotes confidence interval.

†The reference group consists of adolescents and women who did not receive prenatal care because they did not know they were pregnant.

histories have been contradictory.[2-4,9,10] Misclassification of both spontaneous abortion and cocaine use may account for the inconsistent results. Recall of previous spontaneous abortions may be unreliable.[22] The extent of cocaine use is likely to be underestimated if it is based on the patients' reports rather than on objective measurements of cocaine and its metabolites. Furthermore, serum and urine tests detect only recent use of cocaine (use within 72 hours of testing), so that intermittent use may not be detected.[23]

In our study, the strongest association was between the detection of cocaine in hair and spontaneous abortion. Hair analysis is an extremely sensitive marker of cocaine use over a period of weeks or months, depending on the length of hair analyzed.[24,25] Positive results may have been more strongly related to spontaneous abortion than positive urine analysis results because hair analysis reflects the patterns of use over a period of several months. There has been concern, however, that passive exposure to cocaine may lead to a false positive result for hair analysis. In order to distinguish between ingested cocaine and passive environmental exposure to the drug, we used a rigorous washing technique. Had there been false positive results, they should have been equally distributed among the two groups and would thus have reduced the magnitude of the observed estimates.

Confirming the previously suggested relation between cigarette smoking and spontaneous abortion,[11,12] we found that the presence of urinary cotinine was more strongly related to pregnancy outcomes than self-reports of current smoking.[26,27] We conclude that substance use early in pregnancy contributes to the occurrence of spontaneous abortion.

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