

Maternal Periconceptional Illicit Drug Use and the Risk of Congenital Malformations

Marleen M. H. J. van Gelder,^{a,b} Jennita Reefhuis,^a Alissa R. Caton,^c Martha M. Werler,^d Charlotte M. Druschel,^c Nel Roeleveld,^b and the National Birth Defects Prevention Study

Background: In 2004, the Survey on Drug Use and Health showed that 5% of American women reported use of an illicit drug during pregnancy. The results of studies determining the association between periconceptional illicit drug use and birth defects have been inconsistent.

Methods: We analyzed data from the National Birth Defects Prevention Study, a case-control study of major birth defects, and assessed all birth defects categories in which there were at least 250 interviewed case mothers. We included 10,241 infants with major congenital malformations (case infants) and 4,967 infants without major congenital malformations (control infants) born between 1997 and 2003 for whom there was a completed maternal interview with detailed information on prenatal illicit drug use and potential confounders. We used multivariable logistic regression to estimate the associations between cannabis, cocaine, and stimulant use in the month before pregnancy or during the first trimester (periconceptional period) and the occurrence of selected birth defects.

Results: In the periconceptional period, 5% of the 15,208 mothers reported any use of illicit drugs. We did not find associations between illicit drug use and most of the 20 eligible categories of congenital malformations. Periconceptional cannabis use seemed to be associated with an increased risk of anencephaly (adjusted odds ratio = 1.7; 95% confidence interval = 0.9–3.4), whereas cocaine use in the periconceptional period was associated with the risk of cleft palate (2.5; 1.1–5.4).

Conclusions: There were very few suggestions of positive associations between periconceptional illicit drug use and the 20 birth defects categories.

(*Epidemiology* 2009;20: 60–66)

Submitted 12 October 2007; accepted 22 April 2008; posted 2 December 2008. From the ^aNational Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA; ^bDepartment of Epidemiology, Biostatistics, and HTA, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; ^cCongenital Malformations Registry, Center for Environmental Health, New York State Department of Health, Troy, NY; ^dSlone Epidemiology Center at Boston University, Boston, MA.

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Correspondence: Jennita Reefhuis, Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities, Mail-Stop E-86, 1600 Clifton Road, Atlanta, GA 30333. E-mail: JReefhuis@cdc.gov.

Copyright © 2008 by Lippincott Williams & Wilkins

ISSN: 1044-3983/09/2001-0060

DOI: 10.1097/EDE.0b013e31818e5930

In the National Household Survey on Drug Use and Health 2003–2004, 10% of American women aged 15–44 years reported use of an illicit drug in the past month.¹ Of pregnant women in the same age group, 4.6% reported any illicit drug use, 3.6% reported cannabis use, and 0.3% cocaine use. Studies recently conducted in the United States report even higher prevalences of prenatal illicit substance use, ranging from 6.2% to 12.4%.^{2–5} Therefore, many births may potentially be affected by illicit drug use, not only in the United States, but also in other countries.

The results from studies assessing the relationship between prenatal illicit drug use and birth defects have been inconsistent. In general, cannabis does not seem to be associated with major congenital anomalies.^{6–8} However, Williams et al⁹ found an increased risk of isolated simple ventricular septal defects after prenatal marijuana use, and Torfs et al¹⁰ reported an increased risk of gastroschisis in the offspring of marijuana users. Periconceptional cocaine use has been associated with cardiovascular abnormalities,^{11,12} gastroschisis,¹³ limb defects,¹⁴ and genitourinary tract anomalies.^{15,16} The relationship between other types of illicit drugs (eg, stimulants and opioids) and major birth defects has not been studied for specific defects. Also, timing of exposure has not been taken into account.

Several biologic mechanisms for the role of prenatal illicit drug use in the pathogenesis of major birth defects have been proposed. One of the most important components in marijuana smoke is carbon monoxide, which is a known teratogen in animal models.^{17,18} A recent study indicated that delta-9-tetrahydrocannabinol (Δ^9 -THC), the most psychoactive agent in marijuana, modulates genes that encode for growth, cell morphology, ion exchange pathways, and apoptosis in placental development.¹⁹ Human and animal studies have suggested that maternal cocaine use might affect embryonic and fetal development through vasoconstriction in maternal and fetal tissues, leading to hypoperfusion and hypoxia.^{14,20,21}

Determining the true associations between illicit drug use and congenital malformations is difficult because illicit drug use is commonly accompanied by other factors that can affect pregnancy outcome, such as smoking, use of alcohol, and poor prenatal care. In this study, we used data from the National Birth Defects Prevention Study (NBDPS) to inves-

tigate the relationship between periconceptional illicit drug use and selected major birth defects, while controlling for the effects of potentially confounding behavioral factors when possible.

METHODS

The National Birth Defects Prevention Study is an ongoing, population-based, case-control study designed to evaluate environmental and genetic risk factors for major congenital malformations. Eligible case infants were identified from birth defects surveillance systems in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. Case records were reviewed by clinical geneticists in each of the centers to determine initial study eligibility, and all infants with a specific defect were reviewed by one clinical geneticist before analyses to ensure consistency across sites and to assess whether case infants had multiple major defects in different organ systems or whether the case infants' defect was isolated (ie, no additional major unrelated birth defects).²² Control infants, liveborn infants without major congenital malformations, were randomly selected from birth certificates or hospital records from the same geographic regions. All mothers of the infants were interviewed by telephone by trained interviewers in either English or Spanish by using a standardized questionnaire between 6 weeks and 24 months after the estimated date of delivery. Questions were asked about demographic characteristics, lifestyle factors, maternal health, and occupational exposures. The enrollment of case and control infants and the methods of the National Birth Defects Prevention Study have been described in detail elsewhere.²³ The participation rates for mothers of case and control infants were 71% and 67%, respectively.

For our analyses, we included case and control infants born from 1 October 1997 through 31 December 2003, whose mothers completed the entire interview. For power purposes, we limited the analyses to birth defects categories in which there were at least 250 cases with completed maternal interviews. A total of 20 birth defects categories met this criterion, including neural tube defects, several congenital heart defects, oral clefts, and certain gastrointestinal defects.

Detailed information on the type, timing, and frequency of reported maternal illicit drug use was available from the questionnaire. We grouped the illicit substances into 5 drug categories, which were largely based on the classification scheme of the National Institute on Drug Abuse.²⁴ Marijuana and hashish were included in the cannabis group. The cocaine group consisted of cocaine and crack cocaine. Amphetamine, methylenedioxymethamphetamine (MDMA or "ecstasy"), and methamphetamine formed the stimulants group. Lysergic acid diethylamide (LSD or "acid"), psilocybin (hallucinogenic mushrooms), and phencyclidine HCl (PCP or "angel dust") were included in the hallucinogens group. The opioids

group consisted of diacetylmorphine (heroin), oxycodone HCl, hydrocodone bitartrate, and methadone. Medical use of marijuana or methadone was included as exposure to cannabis or opioids, respectively. We defined an infant as exposed for a specific illicit drug category if the mother reported use of 1 or more substances included in that illicit drug group at any time during the period starting 1 month before pregnancy to the end of the third month of pregnancy (periconceptional period). Unexposed infants were case and control infants whose mothers did not report use of any illicit drug in the 3 months prior to and during the entire index pregnancy.

Too few infants were exposed to hallucinogens and opioids to estimate the risks of congenital malformations. Infants born to women with preexisting diabetes type 1 or type 2 ($n = 220$) were excluded from the analyses because of the known strong association between this condition and congenital malformations. After exploratory data analyses, we used multivariable logistic regression techniques to study the associations between periconceptional illicit drug use and the selected birth defects. Based on a priori knowledge and the exploratory analyses, we decided to use the same potential confounder set in all models, except when small numbers prevented us from including 1 or more covariates. These maternal confounders were age at delivery, race or ethnicity, level of education, smoking in the periconceptional period, binge drinking (defined as ≥ 4 drinks per episode) in the periconceptional period, prepregnancy body mass index (BMI), and any periconceptional folic acid use. Age at delivery and BMI were used as continuous covariates, unless the relationship between these variables and the defect studied (the natural logarithm of the odds of having a child with the specific birth defect) was not linear; in such cases, age at delivery and BMI were categorized in the analyses of these specific birth defects. The other covariates were added as dichotomous variables, with race or ethnicity categorized as non-Hispanic white or other, and level of education as 0–12 years or 13 years or more. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for periconceptional use of the particular illicit drug category if there were at least 3 exposed cases. When an association was found between an illicit drug category and a specific birth defect, the exposure time window was limited to the etiologically relevant period for that specific birth defect to explore the association further. In subanalyses, we excluded case and control infants who had a first-degree relative with the specific defect that was analyzed. We also conducted stratified analyses for single and multidrug cannabis users and for the frequency of periconceptional cannabis use (incidental use: ≤ 1 time per week; moderate use: > 1 time per week, but < 1 time per day; heavy use: ≥ 1 time per day). All statistical analyses were performed using SPSS version 14.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

A total of 10,241 case infants with selected congenital malformations and 4967 control infants were included in this study. Maternal characteristics for case and control infants are shown in Table 1. In general, case and control infants were comparable regarding the maternal characteristics. Slight differences were seen in race or ethnicity and in household income between case and control mothers. Furthermore, control mothers were less likely than case mothers to have 0–12 years of education, to have preexisting diabetes,

TABLE 1. Maternal Characteristics of Infants With No Major Birth Defects and Case Infants With Selected Birth Defects^a

Maternal Characteristics	Controls (n = 4967) No. (%)	Cases (n = 10,241) No. (%)
Age at Delivery (y)		
<20	552 (11)	1140 (11)
20–24	1105 (22)	2344 (23)
25–29	1293 (26)	2548 (25)
30–34	1328 (27)	2587 (25)
≥35	689 (14)	1622 (16)
Race or ethnicity		
Non-Hispanic white	2995 (60)	6269 (61)
Non-Hispanic black	580 (12)	1022 (10)
Hispanic	1114 (23)	2353 (23)
Other	266 (5)	576 (6)
Education ≤12 y	2072 (42)	4527 (44)
Household income below median ^b	2478 (56)	5469 (58)
Prepregnancy BMI ^c		
Underweight	284 (6)	574 (6)
Normal weight	2695 (57)	5265 (53)
Overweight	1055 (22)	2232 (23)
Obese	734 (15)	1801 (18)
Preexisting diabetes type 1 or 2	25 (1)	195 (2)
Periconceptual folic acid used	2512 (51)	5242 (51)
Smoked in periconceptual period ^d	962 (19)	2223 (22)
Alcohol in periconceptual period ^d	1874 (38)	3902 (38)
Binge drinking in periconceptual period ^d	642 (13)	1345 (13)
Illicit drug use in periconceptual period ^d	214 (4)	483 (5)
Cannabis	190 (4)	420 (4)
Cocaine	28 (1)	77 (1)
Stimulants	28 (1)	58 (1)
Hallucinogens	3 (<1)	13 (<1)
Opioids	3 (<1)	9 (<1)

Data from the National Birth Defects Prevention Study, 1997–2003.

^aOnly case infants with birth defects that were classified in a category with at least 250 cases with completed maternal interviews were included.

^bMedian income: \$40,000.²⁵

^cBMI, classification of the National Institutes of Health: underweight: <18.5 kg/m²; normal weight: 18.5–24.9 kg/m²; overweight: 25.0–29.9 kg/m²; obese: ≥30 kg/m².

^dPericonceptual period: 1 month before pregnancy to the end of the third month of pregnancy.

to be obese before pregnancy, and to smoke in the periconceptual period.

In the last month before pregnancy and during the first trimester, 4.6% of all mothers reported use of an illicit drug: 4.7% of the case mothers and 4.3% of the control mothers. Only 8 mothers refused to answer the illicit drug use questions. Cannabis was the most frequently reported illicit substance (88%), followed by cocaine (15%), and stimulants (15%). Hallucinogen and opioid use were each reported by 2% of the women who reported illicit drug use. The majority of pregnant illicit drug users (84%) used illicit drugs from 1 substance category. A total of 112 (16%) women used illicit drugs from 2 or more different categories. We did not identify a pattern in the types of congenital anomalies in the 15 infants (13 case and 2 control) who were exposed to 3 or more illicit drugs in the periconceptual period.

The crude and adjusted ORs for periconceptual cannabis use and the selected congenital malformations are shown in Table 2. Periconceptual cannabis use seemed to be associated with an increased risk of anencephaly (adjusted OR = 1.7; 95% CI = 0.9–3.4). Restricting the analysis to cannabis use in the first month after conception, during which the neural tube closes, confirmed this finding (adjusted OR = 2.5; 95% CI = 1.3–4.9). Cannabis use in the other months of the periconceptual period was not associated with an increased risk of anencephaly. Analyses restricted to infants without a positive family history for the specific defects or to infants with isolated defects only did not alter these results. No pattern of increasing or decreasing ORs could be detected after stratification for frequency of periconceptual cannabis use, and we did not find any substantial differences in the crude ORs for the selected congenital malformations between women who used only cannabis and women who used cannabis and at least 1 other illicit substance (data not shown).

Because of the small numbers of infants exposed to cocaine and stimulants, we were not able to calculate adjusted ORs for all of the selected birth defects, or we could do so only with a reduced confounder set (Tables 3 and 4). The risk of spina bifida seemed to be increased after periconceptual cocaine use (adjusted OR = 2.2; 95% CI = 0.9–5.4), but we did not see an increased risk for use in the first month after conception, during which the neural tube closes. We observed, however, an increased odds of having a child with cleft palate among women who used cocaine in the periconceptual period (adjusted OR = 2.5; 95% CI = 1.1–5.4). For cocaine use in the third month after conception, during which the 2 palatine shelves fuse with each other, we found an adjusted OR of 6.8 (2.0–23), which was much stronger than the OR estimates for cocaine use in the other months of the periconceptual period. We did not find any increased or decreased ORs for the selected birth defects among stimulant users.

TABLE 2. ORs and CIs for the Association Between Periconceptual Cannabis Use and Selected Birth Defects

Defect	No. of Cases ^a	No. of Cannabis Exposed	OR (95% CI)	
			Crude	Adjusted ^b
None (controls)	4866	189	Reference	Reference
Anencephaly, craniorachischisis	244	12	1.3 (0.7–2.3)	1.7 (0.9–3.4)
Spina bifida	525	20	1.0 (0.6–1.6)	1.0 (0.6–1.6)
Anotia, microtia	287	11	1.0 (0.5–1.8)	1.0 (0.5–2.0)
Dextrotransposition of the great arteries	336	9	0.7 (0.3–1.3)	0.7 (0.3–1.4)
Tetralogy of Fallot	486	19	1.0 (0.6–1.6)	1.1 (0.6–1.8)
Hypoplastic left heart syndrome	247	7	0.7 (0.3–1.6)	0.7 (0.3–1.6)
Coarctation of aorta	433	15	0.9 (0.5–1.5)	1.0 (0.6–1.8)
Pulmonary valve stenosis	582	24	1.1 (0.7–1.7)	1.2 (0.8–1.9)
Perimembranous VSD	927	34	0.9 (0.6–1.4)	0.9 (0.6–1.4)
ASD secundum	943	31	0.8 (0.6–1.2)	0.7 (0.5–1.0)
ASD not otherwise specified	288	14	1.3 (0.7–2.2)	1.2 (0.7–2.2)
Cleft lip ± cleft palate	1269	61	1.2 (0.9–1.7)	1.0 (0.7–1.4)
Cleft palate	677	25	0.9 (0.6–1.4)	0.8 (0.5–1.3)
Esophageal atresia ± tracheoesophageal fistula	329	12	0.9 (0.5–1.7)	1.2 (0.6–2.2)
Anorectal atresia	468	13	0.7 (0.4–1.3)	0.7 (0.4–1.2)
Hypospadias ^c	924	20	0.5 (0.3–0.8)	0.7 (0.4–1.2)
Transverse limb deficiency	315	14	1.2 (0.7–2.0)	1.1 (0.6–2.0)
Craniosynostosis	517	16	0.8 (0.5–1.3)	1.0 (0.5–1.7)
Diaphragmatic hernia	365	19	1.4 (0.8–2.2)	1.3 (0.8–2.2)
Gastroschisis	485	62	3.6 (2.7–4.9)	1.3 (0.9–1.8)

Data from the National Birth Defects Prevention Study, 1997–2003.

^aInfants born to women with preexisting diabetes type 1 or type 2 were excluded.

^bAdjusted for maternal factors: age at delivery, race or ethnicity, level of education, cigarette smoking, binge drinking, prepregnancy BMI, and periconceptual folic acid use.

^cOnly male control infants included (n = 2452; 4.1% exposed).

ASD indicates atrial septal defect; VSD, ventricular septal defect.

We observed increased crude ORs for having a child with gastroschisis for women with periconceptual use of cannabis, cocaine, and stimulants. However, maternal age at delivery was a strong confounder in these estimates, and the adjusted ORs (cannabis: OR = 1.3 [0.9–1.8]; cocaine: OR = 1.0 [0.4–2.4]; stimulants: OR = 1.0 [0.5–2.3]) showed no association between illicit drug use and gastroschisis.

DISCUSSION

Because very few previously conducted studies had sufficient numbers to look at individual birth defects and illicit drug use, this was primarily a hypothesis-generating study. We did not find associations between periconceptual cannabis, cocaine, and stimulant use and the majority of the congenital malformations assessed. However, there were possible associations between periconceptual cannabis use and anencephaly, and between cocaine use and cleft palate.

The National Birth Defects Prevention Study data offered several advantages in studying associations between periconceptual illicit drug use and birth defects. Because of the population-based and multistate ascertainment of case and control infants, the study population was geographically and racially diverse. Due to the large numbers, we were able to include relatively rare congenital malformations in this study.

Many of the defects included have not been studied before in relation to periconceptual illicit substance use. Also, we implemented an extensive standardized interview that included detailed questions on illicit drug use and important covariates. Every effort was made to conduct the postpartum interviews as close to the estimated date of delivery as possible; the average was 10 months after the estimated date of delivery with a range of 1.5–24 months. There was no difference in average time from the estimated date of delivery to the interview between exposed and unexposed subjects, not even after stratification for case/control status.

It is likely that the use of illicit drugs was underestimated in our study and other studies based on self-report. Respondents often falsely deny use because of the social stigma associated with use and fear of judgment or prosecution. Previous studies have shown that questionnaires identify 66%–82% of participants who test positive for drug use through toxicologic screening.^{2,26,27} Misclassification of the exposure status of infants could attenuate the estimates toward the null value if it was nondifferential between case mothers and control mothers, and it probably had a negative effect on the precision of our estimates. The ORs in this analysis would have been overestimated only if control mothers were more likely to deny illicit drug use than case

TABLE 3. ORs and CIs for the Association Between Periconceptional Cocaine Use and Selected Birth Defects

Defect	No. of Cases ^a	No. of Cocaine Exposed	OR (95% CI)	
			Crude	Adjusted
None (controls)	4705	28	Reference	Reference
Anencephaly, craniorachischisis	234	2	1.4 (0.3–6.1)	—
Spina bifida	512	7	2.3 (1.0–5.3)	2.2 (0.9–5.4) ^b
Anotia, microtia	279	3	1.8 (0.5–6.0)	1.8 (0.5–6.2) ^c
Dextrotransposition of the great arteries	328	1	0.5 (0.1–3.8)	—
Tetralogy of Fallot	472	5	1.8 (0.7–4.7)	1.8 (0.7–4.9) ^b
Hypoplastic left heart syndrome	240	0	—	—
Coarctation of aorta	419	1	0.4 (0.1–2.9)	—
Pulmonary valve stenosis	561	3	1.0 (0.3–3.3)	1.2 (0.4–4.1) ^d
Perimembranous VSD	902	9	1.7 (0.8–3.6)	1.4 (0.6–3.2) ^b
ASD secundum	920	8	1.5 (0.7–3.2)	1.1 (0.5–2.5) ^b
ASD not otherwise specified	275	1	0.6 (0.1–4.5)	—
Cleft lip ± cleft palate	1216	8	1.1 (0.5–2.4)	0.9 (0.4–2.1) ^b
Cleft palate	661	9	2.2 (1.1–4.8)	2.5 (1.1–5.4) ^c
Esophageal atresia ± tracheoesophageal fistula	320	3	1.6 (0.5–5.2)	2.0 (0.6–6.7) ^f
Anorectal atresia	456	1	0.4 (0.1–2.7)	—
Hypospadias ^g	907	3	0.6 (0.2–2.1)	0.9 (0.2–3.2) ^h
Transverse limb deficiency	303	2	1.1 (0.3–4.7)	—
Craniosynostosis	505	4	1.3 (0.5–3.8)	1.8 (0.6–5.4) ⁱ
Diaphragmatic hernia	349	3	1.4 (0.4–4.8)	1.5 (0.4–4.8) ⁱ
Gastroschisis	432	9	3.6 (1.7–7.6)	1.0 (0.4–2.4) ^b

Data from the National Birth Defects Prevention Study, 1997–2003.

Infants born to women with preexisting diabetes type 1 or type 2 were excluded.

^aAdjusted for maternal factors: age at delivery, race or ethnicity, level of education, cigarette smoking, binge drinking, prepregnancy BMI, and periconceptional folic acid use.

^bAdjusted for maternal factors: age at delivery, binge drinking, prepregnancy BMI, and periconceptional folic acid use.

^cAdjusted for maternal factors: age at delivery, race or ethnicity, cigarette smoking, binge drinking, prepregnancy BMI, and periconceptional folic acid use.

^dAdjusted for maternal factors: age at delivery, race or ethnicity, level of education, cigarette smoking, binge drinking, and periconceptional folic acid use.

^eAdjusted for maternal factors: age at delivery, race or ethnicity, prepregnancy BMI, and periconceptional folic acid use.

^fOnly male control infants included (n = 2364; 0.5% exposed).

^gAdjusted for maternal factors: age at delivery, level of education, cigarette smoking, binge drinking, and prepregnancy BMI.

^hAdjusted for maternal factors: age at delivery, cigarette smoking, binge drinking, prepregnancy BMI, and periconceptional folic acid use.

ⁱAdjusted for maternal factors: race or ethnicity, level of education, prepregnancy BMI, and periconceptional folic acid use.

ASD indicates atrial septal defect; VSD, ventricular septal defect.

mothers. Unintentional denial in the form of incomplete recall might also have been an issue in this study. However, among case-control studies of pregnancy outcome, few studies have reported evidence of recall bias.

In this study, we defined an infant as exposed if the mother reported illicit drug use in the period from 1 month before conception through the third month of pregnancy. The month before pregnancy was included because half of the pregnancies in the United States are unintended,²⁸ and such pregnancies are expected to be more prevalent among women who use illicit drugs.²⁹ It would also reduce social desirability bias due to women reporting abandonment of unhealthy behaviors in the first month of pregnancy. Because we collapsed the exposure data for the 4-month period in which most congenital malformations originate, we did not know exactly at what time the women used the illicit drug. This could have led to underestimation or overestimation of our ORs because sporadic users might not have used a drug in the relevant exposure time window for the specific birth defect. Nevertheless, the associa-

tions between periconceptional cannabis and cocaine use and anencephaly and cleft palate, respectively, were found to be strongest in the etiologically relevant periods, indicating that the OR estimates for these associations in the entire periconceptional period were not overestimated.

Combinations of illicit substances can enhance the pharmacologic properties and physical effects of their components. Therefore, it can be hypothesized that certain combinations of illicit drugs could cause a specific congenital malformation. Because just a few women used cannabis and a second illicit substance, we were not able to calculate adjusted ORs for multidrug cannabis users. However, there was no pattern of higher crude ORs among multidrug cannabis users compared with single-drug cannabis users. Furthermore, we did not find a pattern of defects for various combinations of substances among the infants exposed to 3 or more illicit drugs. Nevertheless, it is striking that among the 15 women who used illicit drugs from at least 3 different categories only 2 were control mothers.

TABLE 4. ORs and 95% CIs for the Association Between Periconceptual Stimulant Use and Selected Birth Defects

Defect	No. of Cases ^a	No. of Stimulants Exposed	OR (95% CI)	
			Crude	Adjusted
None	4704	27	Reference	Reference
Anencephaly, craniorachischisis	235	3	2.2 (0.7–7.4)	2.4 (0.7–8.1) ^b
Spina bifida	508	3	1.0 (0.3–3.4)	1.1 (0.3–3.7) ^c
Anotia, microtia	277	1	0.6 (0.1–4.6)	—
Dextrotransposition of the great arteries	329	2	1.1 (0.3–4.5)	—
Tetralogy of Fallot	468	1	0.4 (0.1–2.7)	—
Hypoplastic left heart syndrome	240	0	—	—
Coarctation of aorta	420	2	0.8 (0.2–3.5)	—
Pulmonary valve stenosis	559	1	0.4 (0.0–2.7)	—
Perimembranous VSD	898	5	1.0 (0.4–2.5)	1.1 (0.4–2.9) ^d
ASD secundum	917	5	1.0 (0.4–2.5)	0.8 (0.3–2.0) ^e
ASD not otherwise specified	276	2	1.3 (0.3–5.3)	—
Cleft lip ± cleft palate	1217	9	1.3 (0.6–2.8)	1.0 (0.5–2.3) ^f
Cleft palate	656	4	1.1 (0.4–3.1)	1.2 (0.4–3.5) ^g
Esophageal atresia ± tracheoesophageal fistula	318	1	0.5 (0.1–4.0)	—
Anorectal atresia	458	3	1.1 (0.3–3.8)	1.1 (0.3–3.8) ^h
Hypospadias ⁱ	908	4	0.6 (0.2–1.7)	0.9 (0.3–2.8) ^f
Transverse limb deficiency	304	3	1.7 (0.5–5.7)	1.7 (0.5–5.9) ^j
Craniosynostosis	502	1	0.3 (0.0–2.6)	—
Diaphragmatic hernia	350	4	2.0 (0.7–5.8)	2.0 (0.7–5.8) ^k
Gastroschisis	432	9	3.7 (1.7–7.9)	1.0 (0.5–2.3) ^l

Data from the National Birth Defects Prevention Study, 1997–2003.

^aInfants born to women with preexisting diabetes type 1 or type 2 were excluded.

^bAdjusted for maternal factors: age at delivery, race or ethnicity, level of education, binge drinking, prepregnancy BMI, and periconceptual folic acid use.

^cAdjusted for maternal factors: age at delivery, race or ethnicity, cigarette smoking, binge drinking, and prepregnancy BMI.

^dAdjusted for maternal factors: age at delivery, binge drinking, prepregnancy BMI, and periconceptual folic acid use.

^eAdjusted for maternal factors: age at delivery, race or ethnicity, level of education, cigarette smoking, and prepregnancy BMI.

^fAdjusted for maternal factors: age at delivery, race or ethnicity, cigarette smoking, binge drinking, prepregnancy BMI, and periconceptual folic acid use.

^gAdjusted for maternal factors: level of education, binge drinking, prepregnancy BMI, and periconceptual folic acid use.

^hAdjusted for maternal factors: age at delivery, level of education, binge drinking, prepregnancy BMI, and periconceptual folic acid use.

ⁱOnly male control infants included (n = 2369; 0.8% exposed).

^jAdjusted for maternal factors: age at delivery, cigarette smoking, binge drinking, and prepregnancy BMI.

^kAdjusted for maternal factors: race or ethnicity, level of education, prepregnancy BMI, and periconceptual folic acid use.

^lAdjusted for maternal factors: age at delivery, race or ethnicity, level of education, cigarette smoking, binge drinking, prepregnancy BMI, and periconceptual folic acid use.

ASD indicates atrial septal defect; VSD, ventricular septal defect.

Because we selected 3 exposures of interest and 20 outcomes, it is possible that the associations found were due to chance. The fact that the associations were strongest in the etiologically relevant periods, however, might indicate causality. Additionally, biologic explanations for these associations can be hypothesized. Δ^9 -THC can bind and lead to inappropriate activation of the CB₁ and CB₂ receptor, the 2 cannabinoid receptors known to date.¹⁹ In the early rat embryo, CB₁ receptor messenger RNA is expressed in some cells of the neural tube.³⁰ Because Δ^9 -THC crosses the placenta,³¹ the expression of CB₁ receptor messenger RNA suggests that exogenous cannabinoids might affect the developmental process of the neural tube, leading to neural tube defects. Prenatal marijuana exposure has been associated with neural tube defects in hamsters and rabbits.³² Vasoconstriction and sudden hypertension caused by cocaine use may interrupt fetal blood supply^{14,33} and could, therefore, result in an increased risk of cleft palate by decreasing the supply of

essential nutrients to embryonic tissues.³⁴ We did not identify animal studies in which cocaine exposure was associated with cleft palate in particular.

Some alternative explanations could also be suggested for the associations found. Because anencephaly is diagnosed relatively early in pregnancy, women may choose an induced abortion, but cannabis users might get prenatal care too late for them to do so. However, we did not find a difference in the rate of induced abortions between exposed and unexposed anencephaly cases (41.7% versus 41.4%). Reverse causation bias can also be excluded because we found an increased risk for anencephaly only if cannabis was used in the relevant exposure period (the first month after conception). Furthermore, none of the exposed anencephaly cases was exposed to known teratogenic medications, excluding a confounding effect of medication use. One of the cocaine-exposed cleft palate cases was exposed to phenytoin and phenobarbital, anticonvulsants that have been associated with orofacial

clefts.³⁵ If we exclude this case from the analyses, however, the adjusted OR is still increased (2.2; 1.0–4.9). Potential differential recall associated with time to interview might also explain the positive associations. On average, the mothers of unexposed anencephaly cases were interviewed sooner after the estimated date of delivery than cannabis-using anencephaly case mothers (10 versus 13 months, $P = 0.10$). However, it is unlikely that differential recall would be restricted to anencephaly cases only. For cleft palate cases, we did not see differences in the average time to interview between cocaine-exposed and unexposed mothers.

The present findings showed very few positive associations between periconceptual illicit drug use and selected birth defects. Although the number of infants exposed to cocaine and stimulants was low, the statistical power of the data was sufficient to rule out 2- to 4-fold or greater increases in the risk of the selected birth defects. Cannabis use may be associated with an increased risk of anencephaly in offspring, and the risk of cleft palate appears to be increased for infants exposed to cocaine in the periconceptual period.

ACKNOWLEDGMENTS

The authors thank all the parents who participated in the National Birth Defects Prevention Study and all the staff at the Centers for Birth Defects Research and Prevention. The authors also thank Owen Devine and Peggy Honein for their contributions to this paper.

REFERENCES

- Substance Abuse and Mental Health Services Administration. Results from the 2004 National Survey on Drug Use and Health: National Findings. NSDUH Series H-28, SMA 05-4062. Rockville: Office of Applied Studies; 2005.
- Bauer CR, Langer JC, Shankaran S, et al. Acute neonatal effects of cocaine exposure during pregnancy. *Arch Pediatr Adolesc Med.* 2005; 159:824–834.
- Behnke M, Eyler FD, Garvan CW, et al. The search for congenital malformations in newborns with fetal cocaine exposure. *Pediatrics.* 2001;107:E74.
- Arria AM, Derauf C, Lagasse LL, et al. Methamphetamine and other substance use during pregnancy: preliminary estimates from the Infant Development, Environment, and Lifestyle (IDEAL) study. *Matern Child Health J.* 2006;10:293–302.
- El-Mohandes A, Herman AA, Nabil El-Khorazaty M, et al. Prenatal care reduces the impact of illicit drug use on perinatal outcomes. *J Perinatol.* 2003;23:354–360.
- Shaw GM, Velie EM, Morland KB. Parental recreational drug use and risk for neural tube defects. *Am J Epidemiol.* 1996;144:1155–1160.
- Witter FR, Niebyl JR. Marijuana use in pregnancy and pregnancy outcome. *Am J Perinatol.* 1990;7:36–38.
- Lee MJ. Marijuana and tobacco use in pregnancy. *Obstet Gynecol Clin North Am.* 1998;25:65–83.
- Williams LJ, Correa A, Rasmussen S. Maternal lifestyle factors and risk for ventricular septal defects. *Birth Defects Res Part A Clin Mol Teratol.* 2004;70:59–64.
- Torfis CP, Velie EM, Oechsli FW, et al. A population-based study of gastroschisis: demographic, pregnancy, and lifestyle risk factors. *Teratology.* 1994;50:44–53.
- Lipshultz SE, Frassica JJ, Orav EJ. Cardiovascular abnormalities in infants prenatally exposed to cocaine. *J Pediatr.* 1991;118:44–51.
- Shaw GM, Malcoe LH, Lammer EJ, et al. Maternal use of cocaine during pregnancy and congenital cardiac anomalies (letter). *J Pediatr.* 1991;118:167–168.
- Morrison JJ, Chitty LS, Peebles D, et al. Recreational drugs and fetal gastroschisis: maternal hair analysis in the peri-conceptual period and during pregnancy. *BJOG.* 2005;112:1022–1025.
- Hoyme HE, Jones KL, Dixon SD, et al. Prenatal cocaine exposure and fetal vascular disruption. *Pediatrics.* 1990;85:743–747.
- Chavez GF, Mulinare J, Cordero JF. Maternal cocaine use during early pregnancy as a risk factor for congenital urogenital anomalies. *JAMA.* 1989;262:795–798.
- Battin M, Albersheim S, Newman D. Congenital genitourinary tract abnormalities following cocaine exposure in utero. *Am J Perinatol.* 1995;12:425–428.
- Singh J. Gastroschisis is caused by the combination of carbon monoxide and protein-zinc deficiencies in mice. *Birth Defects Res Part B Dev Reprod Toxicol.* 2003;68:355–362.
- Alexander PG, Tuan RS. Carbon monoxide-induced axial skeletal dysmorphogenesis in the chick embryo. *Birth Defects Res Part A Clin Mol Teratol.* 2003;67:219–230.
- Khare M, Taylor AH, Konje JC, et al. Delta9-tetrahydrocannabinol inhibits cytotrophoblast cell proliferation and modulates gene transcription. *Mol Hum Reprod.* 2006;12:321–333.
- Webster WS, Brown-Woodman PD. Cocaine as a cause of congenital malformations of vascular origin: experimental evidence in the rat. *Teratology.* 1990;41:689–697.
- Jones KL. Developmental pathogenesis of defects associated with prenatal cocaine exposure: fetal vascular disruption. *Clin Perinatol.* 1991; 18:139–146.
- Rasmussen SA, Olney RS, Holmes LB, et al. Guidelines for case classification for the National Birth Defects Prevention Study. *Birth Defects Res Part A Clin Mol Teratol.* 2003;67:193–201.
- Yoon PW, Rasmussen SA, Lynberg MC, et al. The National Birth Defects Prevention Study. *Public Health Rep.* 2001;116(suppl 1):32–40.
- National Institute on Drug Abuse. Commonly abused drugs [National Institute on Drug Abuse web site]. December 7, 2004. Available at: <http://www.drugabuse.gov/DrugPages/DrugsofAbuse.html>. Accessed July 11, 2006.
- U.S. Census Bureau. Income 2001 [U.S. Census Bureau web site]. May 13, 2004. Available at: <http://www.census.gov/hhes/income/income01/statemhi.html>. Accessed September 19, 2006.
- Lester BM, ElSohly M, Wright LL, et al. The Maternal Lifestyle Study: drug use by meconium toxicology and maternal self-report. *Pediatrics.* 2001;107:309–317.
- Eyler FD, Behnke M, Wobie K, et al. Relative ability of biologic specimens and interviews to detect prenatal cocaine use. *Neurotoxicol Teratol.* 2005;27:677–687.
- Finer LB, Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. *Perspect Sex Reprod Health.* 2006; 38:90–96.
- Than LC, Honein MA, Watkins ML, et al. Intent to become pregnant as a predictor of exposures during pregnancy: is there a relation? *J Reprod Med.* 2005;50:389–396.
- Buckley NE, Hansson S, Harta G, et al. Expression of the CB1 and CB2 receptor messenger RNAs during embryonic development in the rat. *Neuroscience.* 1998;82:1131–1149.
- Hatch EE, Bracken MB. Effect of marijuana use in pregnancy on fetal growth. *Am J Epidemiol.* 1986;124:986–993.
- Geber WF, Schramm LC. Effect of marijuana extract on fetal hamsters and rabbits. *Toxicol Appl Pharmacol.* 1969;14:276–282.
- Bingol N, Fuchs M, Diaz V, et al. Teratogenicity of cocaine in humans. *J Pediatr.* 1987;110:93–96.
- van Rooij IA, Wegerif MJ, Roelofs HM, et al. Smoking, genetic polymorphisms in biotransformation enzymes, and nonsyndromic oral clefting: a gene-environment interaction. *Epidemiology.* 2001;12:502–507.
- Kaneko S, Battino D, Andermann E, et al. Congenital malformations due to antiepileptic drugs. *Epilepsy Res.* 1999;33:145–158.