

Parental Recreational Drug Use and Risk for Neural Tube Defects

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The authors investigated whether maternal or paternal periconceptional use of recreational drugs increased the risk of having neural tube defect (NTD)-affected pregnancies using a population-based case-control study of fetuses and liveborn infants with NTDs among 1989–1991 California births. Face-to-face interviews were conducted with mothers of 538 (88% of eligible) NTD cases and 539 (88%) nonmalformed controls, usually within 5 months of delivery. Periconceptional maternal use of cocaine (odds ratio (OR) = 0.74, 95% confidence interval (CI) 0.40–1.4), amphetamines/speed (OR = 0.68, 95% CI 0.39–1.2), or marijuana (OR = 0.64, 95% CI 0.43–0.95) or preconceptional use of alcohol as <1 drink/day (OR = 0.80, 95% CI 0.62–1.0) or ≥1 drink/day (OR = 0.69, 95% CI 0.42–1.2) or of cigarettes as <1 pack/day (OR = 0.90, 95% CI 0.65–1.2) or ≥1 pack/day (OR = 0.59, 95% CI 0.36–0.96) did not increase the risk for delivering NTD-affected offspring. Risks were not substantially altered after adjustment for maternal age, race/ethnicity, vitamin use, education, and household income. Increased NTD risk was also not generally associated with paternal drug use. The authors could not discern whether the decreased risks observed for these maternal exposures reflected a true association or were due to reporting bias, a disproportionate number of drug-exposed NTD cases among spontaneous abortuses that could not be ascertained, or some other bias. *Am J Epidemiol* 1996;144:1155–60.

abnormalities; anencephaly; etiology; pregnancy; spina bifida cystica; teratogens

Neural tube defects (NTDs), specifically anencephaly and spina bifida, are common congenital anomalies that substantially contribute to childhood morbidity and infant mortality (1). Several factors have been associated with the risk for NTDs in offspring, including socioeconomic class, maternal illness or medication use during pregnancy, and maternal diet or vitamin intake (1). A 50 percent or more reduction in NTD risk associated with maternal periconceptional folic acid supplementation (2, 3) is promising but nonetheless indicates that a sizable proportion of NTDs remain etiologically unexplained. NTDs likely have a genetic etiology as well (4), but single gene disorders account for only a small percentage of NTDs (5). The embryonic development of the neural tube appears to be sensitive to exogenous factors. Recreational drug use is common among reproductive aged women and men in the United States (6). Both maternal and paternal exposures to selected drugs have been postulated to contribute to the etiology of congenital anomalies

(7–9) and to other adverse pregnancy outcomes. A paucity of data, however, exists regarding potential risks for specific congenital anomalies, with nearly no data available for possible NTD risks associated with maternal or paternal drug use (7, 10). We examined data from a large population-based case-control study to investigate whether parental periconceptional drug use increased the risk for NTDs among offspring.

MATERIALS AND METHODS

For this case-control study, details of which appear elsewhere (11), infants or fetuses with a NTD (anencephaly, spina bifida cystica, craniorachischisis, or iniencephaly) were ascertained by the California Birth Defects Monitoring Program (12). Medical records were reviewed, including ultrasonography, at all hospitals and genetics clinics for infants/fetuses delivered in a selected California county and whose mother gave her residence as California. Singleton fetuses and liveborn infants diagnosed with a NTD among the cohort of 708,129 births (includes fetal deaths) between June 1989 and May 1991 and fetuses diagnosed prenatally with a NTD and electively terminated between February 1989 and January 1991 were eligible. Ascertained were 653 singleton infants/fetuses with a NTD. Controls were randomly selected from each area hospital in proportion to the hospital's estimated contribution to the total population of infants born alive in a given

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Abbreviations: CI, confidence interval; NTD, neural tube defect; OR, odds ratio

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month from June 1989 to May 1991. Eligible were 644 singleton infants who were born without a reportable congenital anomaly (12) and whose mother was a California resident.

Interviews with mothers were conducted in English (74 percent) or Spanish (26 percent), primarily face-to-face (95 percent). We excluded women who only spoke languages other than English or Spanish (29 cases and 32 controls), as well as 12 women who had a previous NTD-affected pregnancy. Interviews were completed with mothers of 538 (87.8 percent) cases and 539 (88.2 percent) controls at an average of 4.9 months for cases and 4.6 months for controls after the actual or estimated date of term delivery. Information was unavailable for 6.9 percent of case and 6.2 percent of control mothers who refused to be interviewed and from approximately 5 percent of case and control mothers who could not be located. Nonparticipants were similar to study participants in maternal race/ethnicity and age.

To assist women in remembering exposures/events, an interviewer presented each woman with an individualized calendar marked by four time periods: 3 months before conception, 3 months after conception, and the subsequent two trimesters of pregnancy. The date of conception was determined using gestational age estimated primarily from the date of the last menstrual period and, in some circumstances, from ultrasound results and physical examination. The average 2-hour interview elicited information on medical, reproductive, occupational, and family history as well as aspects about her hobbies, vitamin intake, and use of cigarettes and alcohol. With respect to illicit drug use (hereafter referred to as drug use), women were asked, "In the 3 months before you became pregnant, did you take [DRUG] at least once?" "In the first 3 months of your pregnancy, did you take [DRUG] at least once?" These questions were asked for each of the following: amphetamine/speed, lysergic acid diethylamide (LSD), phencyclidine (angel dust, PCP), marijuana/hashish, methadone, heroin, cocaine/crack, synthetic/designer, psilocybin/mushrooms/peyote, or inhalants. If a woman responded, "Yes," she was asked, "How often did you use [DRUG]?" Women were similarly questioned about the baby's father's drug use in the 3 months before pregnancy. Maternal drug use was unknown for 11 cases (for one case, the interview was not completed; for six cases, the interviewer skipped one or more drug use questions; and for four cases, the mother said she did not know or was unfamiliar with the drug in question) and five controls (for two controls, the interviewer skipped one or more drug use questions, and for three controls, the mother said she did not know or was unfamiliar with the drug in

question), and paternal drug use was unknown for 24 cases and 18 controls. None of the missing information was due to the mother's stating that she chose not to respond.

The odds ratio and its 95 percent confidence interval were computed using EGRET (13). The risk of a NTD-affected pregnancy was estimated from maternal drug use (for the period 3 months before through 3 months after conception), from maternal alcohol or cigarette use (for either 3-month period before or after conception), and from paternal drug use (for the period 3 months before conception). Risk was estimated by comparing users of a particular drug with nonusers of that drug. Considered as potential covariates were maternal race/ethnicity (Hispanic, non-Hispanic white, black, other), age (years), education (<high school, high school graduate, 2- or 4-year college graduate), household income (<\$10,000, \$10,000-\$29,999, \$30,000-\$49,999, \geq \$50,000), and use of multivitamins containing folic acid (for the period 3 months before and after conception).

RESULTS

Case mothers, compared with control mothers, were more likely to be Hispanic (49 vs. 36 percent), to have a household income under \$10,000 (25 vs. 15 percent), to be less than 25 years of age (42 vs. 33 percent), and less likely to have graduated from college (17 vs. 28 percent). In the period 3 months before or after conception, 15 percent of all women used cocaine, speed, marijuana, or another drug. In the 3 months before conception, 55 percent used alcohol, and 26 percent smoked cigarettes. Case and control mothers who used drugs, compared with those who did not, were less likely to be college graduates and more likely to be white, younger, multigravidas, vitamin users, smokers, or alcohol users. Among both case and control mothers who used alcohol or smoked cigarettes in the first trimester, the use of drugs was two- to fourfold more common compared with all study mothers.

The risks of having a NTD-affected pregnancy from maternal drug use are displayed in table 1. Elevated risks were not found for any of the investigated substances, including alcohol and cigarette use. In fact, nearly all risk estimates were less than 1.0. Analyses of drug use only prior to conception did not reveal substantially different risk estimates from those observed for use only in the first trimester. Almost all women (two women began use in the first trimester) who reported use in the first trimester also reported use preconceptionally, and approximately 60 percent (41 of 70 case and 55 of 92 control mothers) who used preconceptionally also reported use in the first trimester. Restricting analyses to those women who more

TABLE 1. Relative risks (odds ratios) for a neural tube defects-affected pregnancy from maternal periconceptional* use of selected drug substances, including alcohol and cigarette smoking, California, 1989–1991

Substance used	No. of cases	No. of controls	Odds ratio†	95% confidence interval	Adjusted odds ratio‡	95% confidence interval
Cocaine/crack	21	28	0.74	0.40–1.4	0.93	0.46–1.9
Marijuana/hash	49	73	0.64	0.43–0.95	0.74	0.46–1.2
Amphetamine/speed	25	36	0.68	0.39–1.2	0.92	0.48–1.7
LSD,§ PCP,§ methadone/heroin, synthetic/designer, psilocybin/mushrooms/peyote, inhalants	10	12	0.84	0.33–2.1	0.94	0.36–2.4
Any of above	70	94	0.72	0.51–1.0	0.79	0.54–1.2
Alcohol (3 months before conception)						
<1 drink/day	245	269	0.80	0.62–1.0	1.0	0.77–1.4
≥1 drink/day	34	43	0.69	0.42–1.2	1.1	0.61–1.8
≥5 drinks on one occasion	114	105	0.95	0.69–1.3	1.3	0.92–1.8
Alcohol (first trimester)						
<1 drink/day	138	175	0.72	0.55–0.95	0.89	0.67–1.2
≥1 drink/day	12	10	1.1	0.44–2.8	1.7	0.66–4.5
≥5 drinks on one occasion	49	50	0.90	0.59–1.4	1.1	0.70–1.7
Cigarettes (3 months before conception)						
1–19/day	95	100	0.90	0.65–1.2	0.89	0.62–1.3
≥20/day	31	50	0.59	0.36–0.96	0.62	0.36–1.1
Cigarettes (first trimester)						
1–19/day	73	87	0.80	0.56–1.1	0.90	0.61–1.3
≥20/day	19	29	0.62	0.33–1.2	0.69	0.35–1.4

* Refers to any use in the period 3 months before through 3 months after conception unless otherwise indicated

† Comparison group includes those not exposed to the single substance in question

‡ Adjusted for maternal vitamin use, race/ethnicity, education, income, age, and each of the other variables included in the table. Risk estimates adjusted for cigarette and alcohol use considered only women who used these substances in the first trimester.

§ LSD, lysergic acid diethylamide; PCP, phencyclidine.

frequently (e.g., more than once/month) used each particular drug substance, other than cigarettes or alcohol, did not substantially change the observed risk pattern (not shown). Among women who used substances other than cigarettes or alcohol, 37 percent ($n = 26$) of cases and 45 percent ($n = 42$) of controls used more than one drug. These polydrug users were also not at increased risk to have a NTD-affected pregnancy. Simultaneous adjustment for relevant covariates (see Materials and Methods) and for the potential confounding influence of other drug use was performed. With the exception of prepregnancy alcohol consumption, adjusted estimates were not substantially different from their crude counterparts for use of each particular substance (table 1). Changing the reference group to include only women (201 case and 171 control mothers) who did not use any drug, including alcohol and tobacco, during the 6-month periconceptional period did not reveal substantially different risk estimates for the drugs listed in table 1.

Increased NTD risks were also not observed for paternal drug use as reported by case and control mothers, except for an elevated odds ratio associated with paternal heroin use (table 2). Analyses restricted

to fathers who more frequently (e.g., more than once/month) used a drug showed a risk pattern similar to that for all users of that drug. Among users, 47 percent ($n = 58$) of case and 40 percent ($n = 56$) of control fathers used more than one drug. These polydrug users were also not at additional increased risk to father NTD-affected offspring. Simultaneous adjustment for relevant covariates, including the potential confounding influence of other paternal drug use, revealed only minor changes to the risk estimates for most of the drug use groups (not shown). The adjusted risk estimate for paternal heroin use was reduced to 2.3 (95 percent confidence interval 0.42–12.3). The risk estimate for amphetamine/speed use was modified by household income, with the risk highest in the highest income group; data were too sparse, however, to adequately compute adjusted risk estimates for each household income group.

Analyses restricted to the circumstance where both the mother and the father used at least one drug (other than cigarettes and alcohol) or where either parent used at least one drug did not show increased risks relative to those pregnancies where neither parent used (table 3). In addition, both parents using at least one

TABLE 2. Relative risks (odds ratios) for a neural tube defects-affected pregnancy from paternal use of drugs in the period 3 months before conception, California, 1989–1991

Substance used	No of cases	No of controls	Odds ratio	95% confidence interval
Cocaine/crack	48	41	1.2	0.76–1.9
Marijuana/hash	101	116	0.86	0.63–1.2
Amphetamine/speed	39	39	1.0	0.62–1.6
Heroin	9	2	4.6	0.92–30.6
LSD,* PCP,* methadone, synthetic/designer, psilocybin/mushrooms/peyote, or inhalants	15	14	1.1	0.49–2.4
Any drug above	124	139	0.88	0.66–1.2

* LSD, lysergic acid diethylamide; PCP, phencyclidine.

TABLE 3. Relative risks (odds ratios) for a neural tube defects-affected pregnancy from parental use of drugs* in the periconceptional period,† California, 1989–1991

	No. of cases	No of controls	Odds ratio	95% confidence interval
Neither parent used drugs*	366	357	Reference	
Both parents used drugs*	54	71	0.74	0.51–1.0
Either parent used drugs*	83	89	0.91	0.65–1.3
Mother only	13	19	0.67	0.33–1.3
Father only	70	70	0.98	0.68–1.4
Missing drug use information	35	22		

* Does not include parental cigarette or alcohol use.

† Three months before through 3 months after conception.

drug more than once per month did not show increased risks (not shown).

DISCUSSION

These results do not reveal an association between maternal or paternal periconceptional use of drugs, including maternal alcohol and cigarette use, and having a NTD-affected pregnancy. In general, the lack of an association persisted even after controlling for potentially relevant covariates.

This is the first study to investigate both maternal and paternal drug use as risk factors for NTDs. Although this study had the advantages of size, a population-based ascertainment of cases and controls, a high participation, and control of relevant confounders, it may have been limited by how drug use information was collected. Studies of potential adverse pregnancy outcomes associated with parental drug use have a number of methodological challenges (10). Self-reported maternal drug use has been shown to be unreliable compared with urine and serum testing (14, 15). For example, Shiono et al. (15) recently observed among a population of women receiving prenatal care that cocaine use anytime during pregnancy was reported by only 8.6 percent of women whose sera were positive for cocaine. Our study did not validate maternal drug use reports. There currently, however, is no

objective standard for obtaining information about retrospective maternal drug use during the first few weeks of pregnancy, the period most relevant to neural tube development. Serum or urine screening in early pregnancy for a large random sample of the population seems nearly impossible. Such screening performed at a time later in gestation may not detect drug metabolites in women who used drugs during an earlier relevant embryologic period and stopped. The results by Shiono et al. (15) also demonstrate this issue. In their study, serum testing during the second trimester identified cocaine metabolites in only 8.9 percent of the women who reported that they had used cocaine during pregnancy. Thus, self-reports of drug use may be the only source of information currently available for early pregnancy use.

The accuracy of self-reported drug use information is likely dependent upon many factors not the least of which is a woman's perceived risk for disclosing her drug use during pregnancy to an interviewer. Each woman who agreed to be interviewed was assured that all information collected about her pregnancy would be held in strict confidence and be used only by research staff for summary purposes. Queries about a woman's drug use were made after approximately two-thirds of the interview had been completed and long after a rapport had been established between

interviewee and interviewer. The extent to which these design aspects improved the quality of drug use information is unknown.

Although it is difficult to make comparisons across studies of drug use prevalence periconceptionally because of large variations in study design, the prevalence that we observed among control mothers for the use of cocaine and marijuana is similar to what others have observed (6, 16, 17). For inaccurate reporting to explain the lack of increased risks among mothers for various drugs, one would need to assume that case mothers reported that they had not used a drug when in fact they had. Even if one then assumed that only case mothers' drug use was underestimated as much has been suggested elsewhere (e.g., cocaine and marijuana use were underestimated by 24 and 16 percent) (14), risk estimates would still not exceed 1.0 for either maternal cocaine or marijuana use. Nevertheless, with respect to periconceptional use of a socially stigmatized drug substance, it is difficult to predict whether case, compared with control, mothers would be more or less likely to report such use. Thus, the lack of increased risks observed will need to be substantiated in other investigations before a more secure inference can be made.

It is also unlikely that our results were substantially biased because of nonparticipation of drug-using case mothers. Assuming that as many as 50 percent of case mothers who did not participate were drug users (not alcohol and tobacco) and that drug use among nonresponding control mothers was similar to that among responding control mothers, the risk estimate for any drug use (table 1) would only be raised from 0.72 to 1.0 under these extreme assumptions.

Maternal alcohol and cigarette use also did not reveal increased NTD risks. A potential association between maternal early pregnancy alcohol intake and NTDs has been described in a clinical series (18), but relatively few epidemiologic studies have provided data on this exposure (19, 20). Our findings regarding maternal cigarette smoking are consistent with some reports that did not find increased NTD risks (21, 22) but contrast with others (20, 23, 24). The results of the current study actually suggested a decreasing risk with an increasing number of cigarettes smoked by the mother.

As an alternative explanation, the decreased risks associated with several drugs, including cigarettes, could have occurred because maternal periconceptional use resulted in selective pregnancy loss of fetuses with NTDs. A greater frequency of NTDs has been noted among spontaneous abortuses than among term infants (1). There is also some evidence for an association between maternal cigarette smoking and

spontaneous abortion risk (25) as well as for an association between maternal cocaine use and spontaneous abortion risk (7).

We did not observe increased NTD risks associated with paternal drug use, with the exception of paternal heroin. Although some plausibility exists for studying paternal drug use and adverse reproductive outcomes (e.g., cocaine use by men has been observed to bind to sperm) (26), nearly no information exists for the potential influence paternal drug use may have on the development of human congenital anomalies. Our paternal drug use findings may have been subject to the accuracy of the information reported by the mother. The accuracy was unknown and was conditional on her knowledge about the father's substance use as well as on her willingness to disclose such information. However, the proportion of control fathers considered drug users in this study compares well with the proportion in other studies that have elicited drug use information directly from men (16, 27).

We could not determine from these data whether the decreased NTD risks associated with the use of drugs and cigarette smoking reflect a true association or were due to reporting bias, the use of prevalent (does not include spontaneous abortuses) rather than incident (includes all conceptuses) NTD cases (i.e., undetected drug-exposed cases among spontaneous abortuses), or some other bias.

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