Effects of Prenatal Methamphetamine Exposure on Behavioral and Cognitive Findings at 7.5 Years of Age

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Objective To examine child behavioral and cognitive outcomes after prenatal exposure to methamphetamine.
Study design We enrolled 412 mother–infant pairs (204 methamphetamine-exposed and 208 unexposed matched comparisons) in the Infant Development, Environment, and Lifestyle study. The 151 children exposed to methamphetamine and 147 comparisons who attended the 7.5-year visit were included. Exposure was determined by maternal self-report and/or positive meconium toxicology. Maternal interviews assessed behavioral and cognitive outcomes using the Conners' Parent Rating Scale–Revised: Short Form.
Results After adjusting for covariates, children exposed to methamphetamine had significantly higher cognitive problems subscale scores than comparisons and were 2.8 times more likely to have cognitive problems scores that were above average on the Conners' Parent Rating Scale–Revised: Short Form. No association between prenatal methamphetamine exposure and behavioral problems, measured by the oppositional, hyperactivity, and attention-deficit/hyperactivity disorder index subscales, were found.
Conclusions Prenatal methamphetamine exposure was associated with increased cognitive problems, which may affect academic achievement and lead to increased negative behavioral outcomes. *(J Pediatr 2014;164:1333-8)*.

Methamphetamine use among women of reproductive age is of continuing concern worldwide. In the US, approximately 6.5% of all females over the age of 12 years and 5% of pregnant women aged 15-44 years reported current illicit drug use.[1] Similar to cocaine, methamphetamine is a psychostimulant that blocks dopamine, serotonin, and norepinephrine reuptake. Methamphetamine use results in increased wakefulness and physical activity, hypertension, tachycardia, confusion, decreased appetite, and extreme weight loss.[2] Prenatal methamphetamine use can also lead to vasoconstriction and a restriction of nutrients and oxygen to the fetus.[3] Additionally, methamphetamine use in adults alters brain structures, resulting in smaller subcortical volumes, and alters the balance of neurotransmitters in the brain, decreasing dopamine receptors.[4] Because methamphetamine can cross the placenta,[5,6] the long-term impact of prenatal methamphetamine exposure from age 5 years into adulthood is uncertain, and the possibility of potentially adverse consequences of prenatal methamphetamine use raises concern.

Limited research is available on the impact of prenatal methamphetamine exposure on child development. One study of prenatal amphetamine exposure followed 65 prenatally exposed children through age 15 years.[7] They found that, by age 4 years, exposed children had lower IQ scores than a normative group of Swedish children. At age 8 years, prenatal exposure predicted problems with peers and aggressive behavior,[8] and by 14 years of age, prenatal exposure was associated with decreased school performance, particularly in math, language, and physical fitness activities.[9] Although this study was longitudinal, it lacked a control group, used a small sample size, included other prenatal drug use, and relied on self-report for exposure.

To overcome these limitations, the Infant Development, Environment, and Lifestyle (IDEAL) study matched exposed and comparison participants on 4 demographic variables and prospectively studied a large group of infants prenatally exposed to methamphetamine. The IDEAL study has already found methamphetamine exposure is associated with multiple maternal psychosocial risks[10]; newborn neurobehavioral patterns of decreased arousal, increased stress, and poor quality of movement[11]; increased prematurity and incidence of small for

ADHD	Attention-deficit/hyperactivity disorder
CPRS-R:S	Conners' Parent Rating Scale–Revised: Short Form
IDEAL	Infant Development, Environment, and Lifestyle
PPVT	Peabody Picture Vocabulary Test
SES	Socioeconomic status

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gestational age[12]; increased neonatal intensive care unit admission and referral to child protective services[13]; more likely to exhibit poor suck and have smaller head circumference and length at birth[13]; decreased length through 3 years[14]; and poor grasping ability at 1 and 3 years.[15]

Additionally, the IDEAL study has found increased emotional reactivity and anxious/depressed problems at 3 and 5 years of age,[16] externalizing and attention-deficit/hyperactivity disorder (ADHD) problems at age 5 years,[16] and subtle differences in outcomes predictive of ADHD at 5.5 years of age[17] and that heavy methamphetamine exposure is associated with subtle deficits in cognitive inhibitory control at age 5.5 years.[18] Given these emotional, behavioral, and cognitive findings, the current study uses Conners' Parent Rating Scale–Revised: Short Form (CPRS-R:S) to examine parental report of oppositional behaviors, cognitive problems, and attention problems, including hyperactivity-impulsivity and other behavioral symptoms associated with ADHD at 7.5 years of age for all children enrolled in the study who attended the 7.5-year visit.

Methods

Detailed methods for the IDEAL study have been previously reported.[19] Briefly, recruitment occurred over a 2-year period from September 2002 to November 2004 at 4 clinical sites (Los Angeles, California; Des Moines, Iowa; Tulsa, Oklahoma; and Honolulu, Hawaii) that had an elevated prevalence of methamphetamine use compared with other areas in the US. The study was approved by the institutional review boards at all participating sites, and informed consent was obtained from all participants. A federal Certificate of Confidentiality was obtained to ensure the confidentiality of maternal drug use and results of meconium drug testing, but any evidence of child abuse or neglect remained reportable.

The study involved screening of 34 833 mother–infant pairs at the time of the infant's birth, of which 26 999 were available and screened for eligibility. After screening for eligibility, 17 961 (66.5%) were eligible for the study. Mothers were excluded if they were under 18 years of age (3.5%, n = 957); used opiates, lysergic acid diethylamide, phencyclidine, or cocaine only during pregnancy (2.2%, n = 583); displayed low cognitive functioning (0.2%, n = 48); were overtly psychotic or had a documented history of psychosis (0.1%, n = 34); or were non–English speaking (17.7%, n = 4773). An additional 222 mothers (0.8%) were excluded for various other reasons including the mother being incarcerated or institutionalized, having a child previously enrolled in the study, or distance from study site was prohibitive for follow-up. Exclusion criteria for infants included critical illness and being unlikely to survive (0.5%, n = 133), multiple birth (4.5%, n = 1219), major life-threatening congenital anomaly or documented chromosomal abnormality associated with mental or neurological deficiency (0.5%, n = 128), and overt clinical evidence of an intrauterine infection (0.07%, n = 2). Of these eligible subjects, 3705 mother–infant pairs (21%) consented to participate in the study.

Among the consented, only mothers with prenatal methamphetamine use and their matched unexposed comparisons were enrolled for longitudinal follow-up (N = 412). There were 204 infants who were prenatally exposed to methamphetamine and identified by maternal self-report of methamphetamine use during this pregnancy and/or positive meconium toxicology. The 208 comparison participants denied methamphetamine use during this pregnancy and had a negative meconium screen. Four additional comparison participants were enrolled with difficult-to-find matched characteristics in the event a family was lost during follow-up. Of the 204 exposed, 146 were identified by self-report only, 50 were identified by self-report and positive toxicology, and 8 denied use but had a positive toxicology screen. The exposed and comparison groups were matched on race, birth weight category (<1500 g, 1500-2500 g, >2500 g), maternal education, and type of insurance as a proxy for socioeconomic status (SES). Only the 298 participants who attended the 7.5-year visit (151 exposed and 147 comparison) are included in the analysis. No significant differences in maternal and neonatal characteristics were found between the 298 participants included and the 114 nonparticipants who did not attend the 7.5-year visit ($P > .05$).

With informed consent, a maternal interview (the Recruitment Lifestyle Interview) was conducted in the hospital to determine the presence or absence of licit and illicit prenatal drug use, information regarding the course of pregnancy, number of prenatal care visits, and sociodemographic information.[20,21] Interviewers were trained and certified in the administration of maternal interviews and used scripted introductions to ensure consistency between sites.

Meconium was collected for all infants. Meconium samples were collected in the nursery and collection began immediately to obtain the first and/or earliest discharge of meconium. In some cases, >1 collection of meconium from an infant was used to ensure that an adequate amount could be tested. The samples were shipped to a central laboratory (United States Drug Testing Laboratory in Des Plaines, Illinois) for analysis of the amphetamine class, cocaine metabolites, cannabinoids, opiates, and cotinine. The specimen was initially screened with a sensitive enzyme multiplied immunoassay test (EMIT II; Dade-Behring, Cupertino, California). If positive results were obtained, the specific drug analyte or metabolite was confirmed through the use of gas chromatography–mass spectrometry. Information on the collection procedures and analysis have been previously reported.[19]

The CPRS-R:S[22] was administered to the caregiver at the 7.5-year visit by certified interviewers aware of exposure status. Caregivers responded to the extent to which each item was true within the past 30 days with 1 of the following responses: not true at all (never, seldom), just a little true (occasionally), pretty much true (often, quite a bit), or very much true (very often, very frequent). The short form uses 4 subscales to assess for varying behavioral outcomes: oppositional, cognitive problems, hyperactivity, and ADHD index. The oppositional subscale highlights children who are likely to break rules, are have problems with persons in