



School-Aged Outcomes following Prenatal Methamphetamine Exposure: 7.5-Year Follow-Up from the Infant Development, Environment, and Lifestyle Study

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Objective To assess the relationship between prenatal methamphetamine exposure (PME) and behavior problems at age 7.5 years and the extent to which early adversity mediated this relationship.

Study design The multicenter, longitudinal Infant Development, Environment, and Lifestyle study enrolled 412 mother-infant pairs at 4 sites. Methamphetamine-exposed participants (n = 204) were identified by self-report and/or gas chromatography/mass spectrometry confirmation of amphetamine and metabolites in infant meconium. Matched participants (n = 208) denied methamphetamine use and had a negative meconium screen. At the 7.5-year follow-up, 290 children with complete Child Behavior Checklist data and an early adversity index score were available for analysis (n = 146 exposed).

Results PME was significantly associated with an increased early adversity index score ($P < .001$) and with increased externalizing, rule-breaking behavior, and aggressive behavior ($P < .05$). Early adversity was also associated with higher externalizing behavior scores. Early adversity significantly mediated the relationship between PME and behavioral problems. After adjusting the mediation model for sex, prenatal tobacco, alcohol, and marijuana exposures, and study site, the association of PME with early adversity remained significant.

Conclusions Though PME is associated with behavioral problems, early adversity may be a strong determinant of behavioral outcome for children exposed to methamphetamine in utero. Early adversity significantly mediated the relationship between PME and behavioral problems. (*J Pediatr* 2016;170:34-8).

Methamphetamine use continues to be prevalent in the US, especially in young adults including women of child bearing age. The number of recent new users of methamphetamine among persons aged 12 or older was 133 000 in 2011, which was greater than the 2010 estimate (107 000). The average age of new users of methamphetamine was 17.8 years.¹ Illicit drug use, including methamphetamine, among women during pregnancy continues to be a persistent problem. Among women aged 15-44 years who were pregnant, 5% were current illicit drug users.¹ Further, the prevalence of methamphetamine abuse during pregnancy in women seeking treatment tripled from 1994-2006, rising to 24% of all pregnant women admitted to federally funded treatment centers.²

Many of the initial studies evaluating prenatal methamphetamine exposure (PME) in children have been cross-sectional rather than longitudinal and very few address the influence of exposure on behavioral concerns. An exception is a small study (n = 66) of Swedish children exposed to amphetamines who were followed from birth to age 14 years. These children demonstrated higher levels of aggression and behavioral problems, poorer psychosocial well-being and lower academic achievement.³⁻⁶ Limitations to these findings included lack of a control/comparison group and a high rate of polydrug exposure.

The Infant Development, Environment, and Lifestyle (IDEAL) study is a prospective, multicenter study of children exposed to methamphetamine designed to address some of the limitations of previous investigations. Neurodevelopmental findings from the IDEAL study have demonstrated increased scores for emotional reactivity and anxious/depressed problems at ages 3 and 5 years, and externalizing and attention deficit hyperactivity disorder problems by age 5 years.⁷ Heavy PME exposure was associated with attention problems and

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CBCL	Child Behavior Checklist
GC/MS	Gas chromatography/mass spectrometry
IDEAL	Infant Development, Environment, and Lifestyle
PME	Prenatal methamphetamine exposure

withdrawn behavior at both ages 3 and 5 years with no effects of PME on the internalizing or total behavior problems scales. Children with PME at 5.5 years of age demonstrated no differences in cognition but did exhibit indicators of risk for attention deficit hyperactivity disorder warranting closer monitoring.⁸

Less is known regarding the associations between PME and long-term neurodevelopmental outcomes in children in the context of adverse environmental conditions. Previous work seeking to determine the extent early adversity mediated the relationship between PME and neurobehavioral disinhibition⁹ used an early adversity index score created using data collected on the children and families between 0 and 3 years of age. Initial work using this adversity index score reported PME was predictive of childhood neurobehavioral disinhibition with early adversity mediating this relationship. Specifically, emotional regulation and behavior control issues at age 5 years and deficits in executive cognitive functioning at age 6.5 years¹⁰ associated with PME was mediated by early adversity.⁹ In addition, the question of other predictors of gains in neurodevelopmental outcomes remains. Manley et al¹¹ evaluated cognitive scores in infants from the Caffeine for Apnea of Prematurity Study at ages 18 months and 5 years. They found that higher maternal and paternal education as well as caregiver employment was independent and additive social variables that predicted gains in cognitive scores in these children.

The current study extends our follow-up findings by evaluating the association between PME and behavioral and emotional control at 7.5 years as determined by the Child Behavior Checklist (CBCL). These findings are evaluated within the context of the early adversity index score based on lifestyle and family conditions from ages 0-3 years to better determine the relationship these factors have on PME and behavioral problems.

Methods

The IDEAL study is a multisite, longitudinal study investigating the effects of PME on childhood outcomes. The recruitment methods have been previously reported for the IDEAL study in detail.¹² Briefly, from September 2002 to November 2004, participants were recruited at the time of delivery from 7 hospitals in 4 geographically diverse, collaborating centers in Los Angeles, CA; Des Moines, IA; Tulsa, OK; and Honolulu, HI. A total of 34 833 mother-infant pairs were screened. Of this population, 26 999 were available to be approached; of which, 17 961 (67%) were eligible for the study. Of the eligible population, 3705 (21%) mother-infant pairs were consented for participation ($n = 204$ PME; $n = 3701$ comparisons). Methamphetamine use was confirmed with meconium tests on all consented infants. Exposure to methamphetamine was determined by self-reported use during this pregnancy and/or a positive meconium screen and gas chromatography/mass spectroscopy (GC/MS) confirmation. Of the 204 subjects in the PME

group, 8 subjects denied methamphetamine use but were identified as exposed by toxicology results only; 196 subjects reported amphetamine use with 146 by self-report only (toxicology was negative) and 50 by self-report and positive toxicology. No exposure to methamphetamine was defined as those denying methamphetamine use during this pregnancy and a negative GC/MS for amphetamine and metabolites. The institutional review boards at all the participating sites approved the study, and all subjects signed an informed consent. Confidentiality of information regarding the mothers' drug use was assured by obtaining a National Institute on Drug Abuse Certificate of Confidentiality, which superseded mandatory reporting of illegal substance use.

A postpartum mother was excluded if she met the following criteria: younger than 18 years of age; used opiates, lysergic acid diethylamide, phencyclidine, or cocaine only during her pregnancy; institutionalized for developmental delay or emotional disorders; was overtly psychotic or had a documented history of psychosis; or was non-English speaking. Exclusion criteria for the infants included critically ill and unlikely to survive, multiple birth delivery, major life-threatening congenital anomaly, documented chromosomal abnormality associated with mental or neurologic deficiency, overt clinical evidence of an intrauterine infection, and sibling previously enrolled in the IDEAL study.

For longitudinal follow-up beginning at 1 month of age, a total of 204 infants were classified as PME (as described in the Methods section) and 208 mother-infant dyads were matched within site on maternal race, infant birth weight, private vs public insurance, and maternal educational status. At the 7.5-year follow-up, 290 (70.4%) subjects with complete CBCL data and an early adversity index score were available for analysis. There were no differences in maternal or newborn characteristics of those included vs those not included in the analysis (**Table I**; available at www.jpeds.com).

Measures

PME was defined by maternal self-reported prenatal methamphetamine use and/or GC/MS confirmation of methamphetamine metabolites in infant meconium.

Procedures and indicators similar to those used by Fisher et al¹³ and Flaherty et al¹⁴ were used to create a single index score to represent early adversity. Postnatal visits occurred at ages 1 month, 1 year, 2 years, 2.5 years, and 3 years such that cumulative measures of adversity were available. In the current study, the early adversity index was the sum of a set of binary indicators, including: (1) any self-reported maternal postnatal substance use through 3 years of age (ie, tobacco, alcohol, marijuana, methamphetamine); (2) any extreme poverty experienced between birth and 3 years of age, as indicated by annual household income less than \$10 000 (representing approximately 50% of the US Department of Health and Human Services poverty line for families with 2-5 members during the years data were collected); (3) any primary caregiver changes through 3 years of age; (4) any reported caregiver sexual or physical abuse through 3 years of age;

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