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EFFECTS OF PRENATAL METHAMPHETAMINE EXPOSURE ON BEHAVIORAL AND COGNITIVE FINDINGS AT 7.5 YEARS

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Abstract

Objective—To examine child behavioral and cognitive outcomes after prenatal exposure to methamphetamine.

Study design—412 mother-infant pairs (204 methamphetamine-exposed and 208 unexposed matched comparisons) were enrolled in the Infant Development, Environment and Lifestyle (IDEAL) 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 Conner's Parent Rating Scale – Revised: Short Form (CPRS-R:S).

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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 CPRS-R:S No association between prenatal methamphetamine exposure and behavioral problems, measured by the oppositional, hyperactivity and ADHD Index subscales, were found.

Conclusion—Prenatal methamphetamine exposure was associated with increased cognitive problems which may impact academic achievement and lead to increased negative behavioral outcomes.

Keywords

amphetamine; ADHD; Conner's

Methamphetamine use among women of reproductive age is of continuing concern worldwide. In the United States, approximately 6.5% of all females over the age of 12 years and 5% of pregnant women ages 15 to 44 years reported current illicit drug use1. 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 alter 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 years7). They found 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, utilized a small sample size, included other prenatal drug use, and relied upon self-report for exposure.

To overcome these limitations, the Infant Development, Environment and Lifestyle (IDEAL) study matched exposed and comparison participants on four 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 gestational age (SGA)(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] 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[16], externalizing and attention-deficit/hyperactivity (ADHD) problems at age 5 years[16], 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 utilizes Conners' Parent Rating Scales – 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 two-year period from September 2002 to November 2004 at four clinical sites (Los Angeles, CA; Des Moines, IA; Tulsa, OK; Honolulu, HI) that had an elevated prevalence of methamphetamine use compared with other areas in the United States. 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 assure 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, 17961 (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 (LSD), phencyclidine (PCP) 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=4 773). An additional 222 mothers (0.8%) were excluded for various other reasons including mother 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 unlikely to survive (0.5%, n=133), multiple birth (4.5%, n=1 219), major life threatening congenital anomaly or documented chromosomal abnormality associated with mental or neurological deficiency (0.5%, n=128), overt clinical evidence of an intrauterine infection (0.07%, n=2). Of these eligible subjects, 3,705 (21%) mother-infant pairs 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). 204 infants were prenatally exposed to methamphetamine and were 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 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 (n=151 exposed, n=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 non-participants 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 utilized scripted introductions to ensure consistency between sites.

Meconium was collected on all infants. Meconium samples were collected in the nursery and began immediately in order to attempt to collect the first and/or earliest discharge of meconium. In some cases, more than one collection of meconium from an infant was used to ensure an adequate amount that could be tested. The samples were shipped to a central laboratory (United States Drug Testing Laboratory in Des Plaines, IL) 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, CA). If positive results were obtained, the specific drug analyte or metabolite was confirmed by gas chromatography-mass spectrometry. Information on the collection procedures and analysis have been previously reported[19].

Conners' Parent Rating Scales – Revised: Short Form (CPRS-R:S)[23] was administered to the caregiver at the 7.5 year visit by certified interviewers aware of exposure status. Caregivers responded to how often each item was true within the past 30 days with one 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 utilizes four 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, have problems with persons in authority, and are more easily angered and annoyed than most children of their age. The cognitive problems subscale contains items related to learning problems (learn slower than children of their age, problems organizing their work) and inattention (difficulty completing tasks or trouble concentrating on tasks that require sustained mental effort). The hyperactivity subscale highlights children who have difficulty sitting still or remaining at the same tasks for very long, feel more restless and impulsive than other children of their age, and need to always be "on the go." The ADHD Index was designed to identify children with symptoms matching the criteria for an ADHD diagnosis in the DSM-IV [22].

The subscales of CPRS-R:S are highly correlated with their matching subscales on the long version (CPRS-R:L) of CPRS-R, ranging from .97 to .98 for males and .96 to .97 for females[(23)]. Additionally, the matching CPRS-R:L subscales maintain high internal reliability in both males and females ages 3 to 7 years, ranging from .86 to .92[(24)]. Researchers also found the CPRS-R maintains high internal consistency (α=.87–.91) in a population of children and adolescents seeking outpatient psychiatric treatment for varying diagnoses[(25)]. The CPRS-R:S oppositional subscale is composed of six items, cognitive problems and hyperactivity are each also composed of six items, and the ADHD Index is composed of 12 items.

STATISTICAL ANALYSES

Maternal and neonatal characteristics (Tables I and II) were considered as potential covariates in the multivariate models and were examined by prenatal methamphetamine exposure status. Means and standard deviations are used for continuous measures and categorical variables are presented as observed counts and percentages. A covariate was included in the multivariate models if it was associated with methamphetamine exposure status and/or the outcome being analyzed (p value <=0.10). A priori covariates included prenatal exposure to alcohol, tobacco, and marijuana; prematurity; sex; and SES. Other variables were examined for inclusion on the basis of published literature, including the Brief Symptom Inventory to assess caregiver psychological symptoms, Home Observation for Measurement of the Environment (HOME) to assess quality of the home, and Peabody Picture Vocabulary Test (PPVT) to assess maternal receptive vocabulary in English. Covariates measures at multiple time points were averaged (e.g., caregiver psychological symptoms, average SES) to provide the best estimate of the child's environment to date. The Brief Symptom Inventory administered at 1 month, 1 year and 3 years yielded an overall score of caregiver psychological symptoms. SES was calculated using the 4-factor Hollingshead Index [(26, 27)] adapted for single-parent and nonnuclear families and averaged across multiple visits from age 1 month through 7.5 years. For descriptive purposes, low SES (Hollingshead V) at recruitment is reported in Table I. There were 13% and 3% missing for the HOME and PPVT, respectively. Multiple imputation using SAS PROC MI was applied (SAS v9.1.3). The results were similar to analyses without imputation and the final model from the imputed dataset was used to retain the full sample. All multivariate models (linear and logistic regression, as appropriate) were adjusted for prenatal exposure to alcohol, tobacco, and marijuana; sex; prematurity; single (no partner); postnatal use of tobacco, alcohol and marijuana; caregiver psychological symptoms; quality of the home; PPVT; age at assessment; average SES and study site. Presented are both the unadjusted and adjusted p-values for methamphetamine exposure status and CPRS-R:S t-scores that were obtained through this process.

All analyses were performed using SPSS v17 (Chicago, Illinois) and SAS v9.1.3 (Cary, NC). Two-sided p-values ≤ 0.05 were used in the analysis, unless otherwise noted.

RESULTS

Table I compares the maternal sociodemographic characteristics, prenatal substance use history, and postnatal substance use by methamphetamine exposure status for the 298 participants included. As expected by study design, there were no differences in race or educational level. Mothers using methamphetamine were of lower SES and less likely to have a partner at birth ($p<0.001$). No differences were observed in maternal age. Although both groups included individuals who used alcohol, tobacco and marijuana during and after pregnancy, women using methamphetamine were more likely to consume tobacco, alcohol and marijuana during pregnancy ($p<0.001$), and more likely to use tobacco after pregnancy ($p=0.005$).

Table II shows the neonatal birth characteristics between the 298 participants in the methamphetamine-exposed and comparison groups. No significant differences between the exposed and comparisons were found in sex, birth weight or birth head circumference. Infants exposed to methamphetamine were more likely to be shorter ($p=0.002$) and more likely to be born earlier ($p=0.002$).

Table III shows the unadjusted and adjusted scores for the effects of methamphetamine exposure on the CPRS-R:S subscales. Unadjusted means show exposure was associated with increased cognitive problems scores ($p=0.011$) and hyperactivity scores ($p=0.023$). After adjusting for covariates, only increased cognitive problems scores ($p=0.048$) remained significantly associated with exposure status. Adjusted means show methamphetamine exposure was not associated with the oppositional, hyperactivity, or ADHD Index subscales.

Table IV shows the odds of scoring on each subscale as a possible problem area, defined as a t-score above 60 (1 standard deviation above the mean), given methamphetamine exposure status. After adjusting for covariates, children exposed to methamphetamine were 2.8 times more likely to have cognitive problems t-scores that were above average on the CPRS-R:S.

DISCUSSION

After adjusting for covariates, among children followed prospectively since birth, we found children age 7.5 years who were prenatally exposed to methamphetamine were significantly more likely to score higher on the cognitive problems subscale on the CPRS-R:S than the comparisons per parent report. No association with prenatal methamphetamine exposure and oppositional behaviors, hyperactivity, or behaviors associated with ADHD was found per parent report.

Our findings are consistent with previous studies, which found that children exposed to methamphetamine performed poorly on cognitive activities[18, 28]. Given numerous brain development processes occur *in utero*, including cell proliferation, cell migration, cell differentiation, and myelination[29], there are various possibilities for prenatal methamphetamine exposure to impact neurodevelopment, and ultimately cognitive outcomes. Our findings are also consistent with neuroimaging research which found volumetric reductions in the caudate nucleus in preschool children prenatally exposed to methamphetamine and suggest the caudate nucleus impacts cognitive control processes[30], as well as with researchers who found decreased putamen, globus pallidus and hippocampus volumes that were correlated with decreased performance on sustained attention and delayed verbal memory and suggest these decreased volumes may contribute to poorer learning[28].

Our findings are also consistent with research of preschool children prenatally exposed to cocaine demonstrating deficits in cognitive skills[31]. Given the similarities in mechanisms of action for cocaine and methamphetamine, theses findings may not seem surprising; however the effects of prenatal cocaine exposure on development are conflicting, with researchers also finding no significant association at age 6 years with prenatal exposure and cognitive deficits or teacher-rated classroom behavior, including attention[32]. Additionally, the aforementioned research has shown the child's environment may mediate cognitive results, with children who were placed in foster or adoptive care scoring similar to unexposed children and those staying with biological mothers scoring below the unexposed children[32]. Given the IDEAL study collected environmental information throughout, the current study was able to adjust for the quality of home life. Controlling for this factor strengthens the results and implies regardless of home life, prenatally exposed children experience increased cognitive problems per parent report.

It should be noted our data differ from previous IDEAL findings of externalizing and attention-deficit/hyperactivity (ADHD) problems at age 5 years[16], and subtle differences in outcomes predictive of ADHD at 5.5 years of age [17]. It is possible the observed differences in the exposed group between these two age periods is secondary to behavioral and attention difficulties dissipated with age or environmental factors. Alternatively these differences could be accounted for, in part, by the current study assessing parent report, whereas the results found at 5.5 years of age utilized child-based measures. Additionally, a high percentage (23.8%) of comparison children received a T-score over 60, representing a significant/possible problem, on the hyperactivity subscale of the CRPS-R:S. Given this percentage is higher than anticipated in an unexposed population, it is less likely we would be able to observe differences in the methamphetamine-exposed group.

The current study utilized CPRS-R:S to assess for ADHD symptoms, however CPRS-R:S is not designed to be the sole criteria for decision making, assessment, or clinical ADHD diagnosis. As a result, elevated scale scores cannot constitute a clinical diagnosis of ADHD. Given the inability and ethical concerns regarding requiring participants to receive testing for ADHD, it is possible the number of participants who truly meet criteria for a clinical diagnosis of ADHD is higher.

CPRS-R:S findings are also based on parental report and the results could be impacted by reporter bias, including an inability to honestly assess the behavior of one's child, not considering particular behaviors troublesome, and the impact of various cultural factors. However, when 212 of these mothers were previously interviewed when the child was 3 years of age, no differences between groups were found on perceived child behavior problems based on parental report[33]. Future research could reduce uncertainty regarding reporter bias by comparing results from the CPRS-R:S with those of the child's teacher utilizing the Conners' Teacher Rating Scale, data the current study unfortunately did not have access to.

Moreover, this study did not examine the relationship between the total amount of methamphetamine used or timing of methamphetamine exposure and the likelihood or severity of problems. Future studies should investigate these possible dose-dependent effects.

Our findings highlight the importance of early identification and intervention for children prenatally exposed to methamphetamine. Cognitive problems, including learning slower than peers, difficulties organizing work and completing tasks, and problems concentrating on tasks that require sustained mental effort, can result in educational deficits during childhood[34]. Although parents receive medical referrals as necessary when their child is born, many parents lack knowledge about services available to their child later in life. Providing psychoeducation to parents of exposed children regarding advocating for individualized educational programs at a young age if they fear their child is exhibiting cognitive problems may improve academic outcomes. In a study of 6–12 year old children, research showed teaching children to advocate for themselves and participate in the IEP process leads to increased academic achievement when compared with students who did not participate[35].

Additionally, cognitive problems linked to inattention predict negative externalizing behaviors during childhood[36], possibly due to the frustration, lack of motivation, and confusion children may experience when compared with their peers. It is also possible future behavioral problems may result from cognitive problems associated with prenatal methamphetamine exposure. Unfortunately, researchers have also found an association between being a victim of physical abuse and exhibiting externalizing behaviors[37], or having certain clinical diagnoses including conduct disorder and oppositional defiant disorder[38]. The long-term impacts of cognitive problems are potentially far reaching. Professionals of varying capacities should encourage parents to monitor their child's development and empower parents to advocate for their child when necessary by providing parents with the necessary knowledge. Additionally, it is uncertain whether significant differences in behavioral and attentional issues will reappear in later years given both issues were previously reported at age 5 and 5.5 years [16, 17]. These findings reiterate the importance of continued follow up of children prenatally exposed to methamphetamine to determine the predictive validity of these deficits. Our study indicates a need to identify those who are prenatally exposed to methamphetamine so that ongoing developmental surveillance can be provided.

Additional studies on how prenatal methamphetamine exposure impacts behavioral and cognitive outcomes during childhood are still necessary. This study did not address whether there is a dose- or time-dependent relationship between methamphetamine exposure and the outcomes. It is also uncertain whether the differences found can be accounted for by more severe concomitant drug use, including tobacco, alcohol, and marijuana, among methamphetamine users.

Identifying substance using pregnant women and availability of comprehensive treatment programs remains a challenge for health care providers. Ongoing education and awareness by professionals is necessary to assist in overcoming the challenge. A nonjudgmental community public health centered approach toward treatment and follow up is essential for successful treatment. Medical professionals providing prenatal services need to make use of community resources available to them for early referral and treatment of pregnant women. Additionally, comorbidities such as concurrent psychiatric conditions need to be treated in an appropriate and timely manner in order to maximize the benefits of drug treatment programs.

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Abbreviations

CPRS-R:S	Conner's Parent Rating Scale – Revised: Short Form
IDEAL	Infant Development, Environment and Lifestyle
SES	Socioeconomic status

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Table 1

Maternal characteristics by methamphetamine exposure

	Number (Percent)/Mean (SD)		
	Exposed (n = 151)	**Comparison (n= 147)**	**P-value**
Race			0.853
White	57 (37.7%)	61 (41.5%)	
Hispanic	32 (21.2%)	31 (21.1%)	
Pacific Islander	29 (19.2%)	24 (16.3%)	
Asian	23 (15.2%)	20 (13.6%)	
Black	5 (3.3%)	8 (5.4%)	
American Indian	5 (3.3%)	3 (2.0%)	
Low SES (Hollingshead V)	50 (33.1%)	15 (10.2%)	<0.001
No partner at birth	85 (56.3%)	48 (32.7%)	<0.001
Education <high school	69 (45.7%)	55 (37.7%)	0.161
Maternal age (years)	25.4 (5.6)	24.5 (5.5)	0.128
Prenatal tobacco use	123 (81.5%)	37 (25.2%)	<0.001
Prenatal alcohol use	50 (33.1%)	20 (13.6%)	<0.001
Prenatal marijuana use	45 (29.8%)	6 (4.1%)	<0.001
Postnatal Characteristics			
Current tobacco use	68 (45.0%)	42 (29.2%)	0.005
Current alcohol use	68 (45.0%)	75 (52.1%)	0.226
Current marijuana use	5 (3.3%)	10 (6.9%)	0.156

Table 2

Neonatal characteristics by methamphetamine exposure

	Number (Percent)/Mean (SD)		
	Exposed (n= 151)	**Comparison (n= 147)**	**P-value**
Sex (boy)	80 (53.0%)	78 (53.1%)	0.989
Birth weight (g)	3182 (629)	3294 (558)	0.103
Birth length (cm)	49.8 (3.6)	51.1 (3.0)	0.002
Birth head circumference (cm)	33.6 (1.8)	33.9 (1.8)	0.157
Gestational age (weeks)	38.3 (2.4)	39.1 (1.8)	0.002

Table 3

CPRS-R T- Scores by methamphetamine exposure

	Mean ± SD			
	Exposed (n = 151)	**Comparison (n= 147)**	**Unadjusted P-Value**	**Adjusted P-value***
Oppositional	54.6 ± 12.6	52.4 ± 10.0	0.096	0.355
Cognitive Problems	54.8 ± 11.8	51.6 ± 9.8	0.011	**0.048**
Hyperactivity	57.2 ± 11.9	54.3 ± 10.3	0.023	0.129
ADHD Index	55.2 ± 10.8	52.9 ± 9.7	0.056	0.226

*Adjusted for prenatal exposure to alcohol, tobacco, and marijuana; prematurity; sex; single (no partner); postnatal use of tobacco, alcohol and marijuana; caregiver psychological symptoms; quality of the home; PPVT; age at assessment; average SES and study site.

Table 4

CPRS-R Significant/Possible Problem (T score >60) by methamphetamine exposure

	Number (Percent)		
	Exposed (n = 151)	**Comparison (n= 147)**	**Odds Ratio* (95% CI)**
Oppositional	39 (25.8%)	29 (19.7%)	1.35 (0.6, 3.0)
Cognitive Problems	43 (28.5%)	25 (17.0%)	**2.80 (1.2, 6.5)**
Hyperactivity	54 (35.8%)	35 (23.8%)	1.54 (0.7, 3.4)
ADHD Index	41 (27.2%)	27 (18.4%)	1.46 (0.6, 3.4)

*Adjusted for prenatal exposure to alcohol, tobacco, and marijuana; prematurity; sex; single (no partner); postnatal use of tobacco, alcohol and marijuana; caregiver psychological symptoms; quality of the home; PPVT; age at assessment; average SES and study site.