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School-Aged Outcomes following Prenatal Methamphetamine Exposure: 7.5 Year Follow-Up From The Infant Development, Environment, and Lifestyle (IDEAL) Study

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Abstract

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 IDEAL 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 (CBCL) 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<0.001) and with increased externalizing, rule-breaking behavior, and aggressive behavior (P<0.05). Early adversity was also associated with higher externalizing behavior scores. Early adversity significantly mediated the relationship between PME and behavioral problems. After

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adjusting the mediation model for sex, prenatal tobacco, alcohol, and marijuana exposures, and study site, the association of PME with early adversity remained significant.

Conclusion—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.

Keywords

Central Nervous System Stimulants; Substance Exposure; Childhood Behavioral Checklist (CBCL)

Methamphetamine use continues to be prevalent in the United States, 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 to 44 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 to 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 methamphetamines 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 Study (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 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 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 disinhibition[9] utilized 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 years [10] associated with PME was mediated by early adversity. [11] Additionally, the question of other predictors of gains in neurodevelopmental outcomes remains. Manley et al[12] evaluated cognitive scores in infants from the Caffeine for Apnea of Prematurity Study (CAP Study) at 18 months and 5 years. They found that higher maternal and paternal education as well as caregiver employment were independent and additive social variables that predicted gains in cognitive scores in these children.

The current study extends our followup 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 0 to 3 years to better determine the relationship these factors have on PME and behavioral problems.

Methods

The Infant Development, Environment, and Lifestyle (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.[13] 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. 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 post-partum mother was excluded if she met the following criteria: younger than 18 years; 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 Study Design) and 208 mother-infant dyads were matched within site on maternal race, infant birth weight, private verses 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 versus 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 gas chromatography/mass spectroscopy confirmation of methamphetamine metabolites in infant meconium.

Procedures and indicators similar to those used by Fisher et al[14] and Flaherty et al[15] were used to create a single index score to represent early adversity. Postnatal visits occurred at 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: (a) any self-reported maternal postnatal substance use through 3 years (i.e., tobacco, alcohol, marijuana, methamphetamine); (b) any extreme poverty experienced between birth and 3 years, as indicated by annual household income less than $10,000 (representing approximately 50% of the U.S. Department of Health and Human Services poverty line for families with two to five members during the years data were collected);(c) any primary caregiver changes through 3 years; (d) any reported caregiver sexual or physical abuse through 3 years; (e) any maternal subscale score on the Brief Symptom Inventory above the clinical cut point [16] through 3 years; (f) maternal depression one standard deviation or greater above the mean from birth through 3 years as indicated by the Beck Depression Inventory [17]; (g) quality of the living environment one standard deviation or greater below the mean at 2.5 years as indicated by the HOME Inventory [18]; (h) community violence one standard deviation or greater above the mean from birth through 3 years as indicated by the Neighborhood Problems section of the Lifestyle Interview and (i) social position one standard deviation or greater below the sample mean from birth through 3 years as indicated by the Index of Social Position, which represents a weighted average of parental occupational status and educational.[19,20]

The Child Behavior Checklist (CBCL) for ages 6 to 18 utilized in this study has been widely used as a method of identifying problem behavior in children.[21] The CBCL was read to the caregiver by a certified interviewer then computer scored to yield measures of internalizing, externalizing and total problems and syndrome scores that aggregate co-occurring problems and are the basis for internalizing(anxious/depressed, somatic complaints, or withdrawn) and externalizing (rule-breaking behavior and aggressive behavior) scores. Higher scores indicate more problems. Following scale developers' recommendations, internalizing, externalizing and total problem scores were standardized (T scores) and raw scores were used for the syndrome scales. Some items on the CBCL are consistent with Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-V) diagnostic categories.

Statistical Analyses

The PROCESS macro for SPSS[22] was used to test for mediation effects. Direct and indirect effects are tested using a regression-based approach. Mediation in this study is defined as a statistically significant indirect effect. A priori infant characteristics included as covariates in the mediation models were sex, prenatal tobacco, alcohol and marijuana exposures, and study site. All analyses were performed using SPSS v17.0.3 (Chicago, Illinois).

Results

A comparison of children studied at 7.5 years of age when compared with those not studied demonstrates no significant differences in birth and maternal demographic characteristics with the exception of a slightly smaller head circumference in the group studied. (Table I)

Maternal demographic data for the groups (n= 146 (71.1%) PME and n=144 (69.2%) comparison subjects) are shown in Table II. Women in the PME group were more likely to have low socioeconomic status (SES) and be without a partner at birth. Further, mothers in the PME group were more likely to use tobacco, alcohol, and marijuana during pregnancy. There were no significant differences in maternal age, or education between the two groups of women. There also were no differences in sex, birth weight, and head circumference (Table II). Though gestational age was younger in the exposed group, both groups had a term mean gestational age. Children in the exposed group had shorter birth length relative to the comparison group.

Children with PME were exposed to significantly more overall early adversity index than comparison children (Table III). Further, the PME group had a higher rate of any extreme poverty, any changes in the primary caregiver of the child and any low social position.

Table IV presents the results of the CBCL assessment. Children with PME at 7.5 years of age had increased externalizing, rule-breaking behavior, and aggressive behavior on the CBCL. The indirect effect of externalizing behavior mediated by early adversity was statistically significant and the total percent mediated was 34%. The indirect effect of rule breaking behavior mediated by early adversity was not significant and the total percent mediated was 26%. The indirect effect of aggressive behavior mediated by early adversity was not significant and the total percent mediated was 29%. PME was associated with increased early adversity ($B=0.98$, $p<.001$, $R^2=.11$). Early adversity was associated with higher externalizing problems at 7.5 years ($B=0.92$, $p<.05$, overall $R^2=.03$).and the direct effect of PME on externalizing problems was not significant ($B=1.75$, $p>.05$). Early adversity was associated with an increase in rule-breaking behavior at 7.5 years ($B=0.64$, $p<.05$, overall $R^2=.04$) and the direct effect of PME on rule-breaking behavior was not significant ($B=1.21$, $p>.05$). Early adversity was associated with an increase in aggressive behavior at 7.5 years ($B=0.77$, $p<.05$, overall $R^2=.04$) and the direct effect of PME on rule breaking behavior was not significant ($B=1.81$, $p>.05$). The association between PME and adversity remained significant with the covariates included in the models, as well as the relationship between early adversity and externalizing problems (Figure; available at www.jpeds.com).

Discussion

This followup study to age 7.5 years extends our understanding of the effects of PME on child behavior. We found that PME was associated with increased scores in the externalizing behavior domain of the CBCL. After adjusting for confounding variables associated with developmental outcome, early adversity appears to be a strong determinate of adverse behavioral outcomes in methamphetamine exposed children. These findings are consistent with previous work that demonstrated PME and early adversity were associated with behavioral and emotional control issues at age 5 years.[11]

The Child Behavior Checklist (CBCL) utilized in this study has been widely used as a method of identifying problem behavior in children[21]. Previous studies utilizing the CBCL have demonstrated that substance exposure was associated with externalizing and internalizing behavior problems in children as young as 3 years old.[23,24] These issues persisted through to school age with specific behavioral syndromes of attention problems at 4, 6, and 9 to 11 years, aggressive behavior at 3 and 7 years, anxiety/depression at 3 and 8 years and withdrawn behavior at 3 years[23]. Additionally, Linares et al[25] utilized the CBCL to demonstrate a probable clinical range for oppositional defiant disorder and attention deficit hyperactivity disorder at 6 years of age in children prenatally exposed to cocaine.

There are a limited number of prenatal drug exposure studies assessing the contribution of early adversity with postnatal outcome. Fisher et al[14] included early postnatal environmental adversity (described as postnatal drug exposure, unstable home and caregiver environment, low SES, caregiver experiences of abuse and psychopathology) as an additional predictor and mediator between maternal cocaine abuse and later negative neurodevelopmental outcomes in children with prenatal cocaine exposure.[14] These findings demonstrated that prenatal drug use predicted the emergence and growth in neurobehavioral disinhibition across adolescence (directly for behavioral dysregulation and indirectly for executive function difficulties via early adversity and behavioral dysregulation). [14] Early adversity uniquely predicted executive function difficulties. [14] Studies have shown that parental methamphetamine use is predictive of an adverse environment with parents reporting that they feel they have created an unsafe and poorly nurturing environment for their children as a result of their methamphetamine use.[26]

Further work has been done to evaluate childhood behavioral problems and early adversity in school- age children with PME. This growing body of literature has demonstrated cognitive and behavioral effects of PME on the growing child, specifically to their brain structure and neurochemistry.[27–29] There is evidence that the microstructural integrity of white matter is disrupted in PME children which coincides with impairment of motor function and aspects of executive function.[29] Other studies have demonstrated memory and attention deficits among children with PME. Chang et al (2004) linked smaller volume subcortical structures (i.e. putamen, globus pallidus, hippocampus, and caudate) with memory and attention deficits among children with PME from 3-16 years old[30]. In previous findings from the IDEAL study, Abar et al[11] examined the extent to which PME was predictive of childhood neurobehavioral disinhibition (ND) and the extent to which early adversity (birth through year 3) mediated this process. At age 6.5 years of age PME was associated with issues regarding behavioral and emotional control at 5 years of age, which was associated with executive function deficits at 6.5 years. Moreover, early adversity significantly mediated the relationship between PME and ND.

There are limitations to this study. First our findings may not generalize to all populations of women who use methamphetamine while pregnant and did not focus on mediators that can minimize the effects of adverse events on child outcomes. Because CBCL findings are based on caregiver report, there could be reporting bias. In addition, our measure of child abuse through caregiver report of Child Protective Services involvement likely underestimates true rates of abuse.

Though PME is associated with behavioral problems, early adversity may be a strong determinant of behavioral outcomes. Early adversity mediated the relationship between behavioral problems and PME. These findings are consistent with previous work that demonstrated PME and early adversity was associated with behavioral and emotional control at 5 years and early adversity mediated the relationship between PME and neurobehavioral disinhibition. The current study only follows behavioral outcomes from birth through 7.5 years; long-term follow-up is needed for a more complete understanding of the developmental, behavioral and social outcomes of PME infants. Further studies regarding the role of adversity in PME infants would need to be conducted to explicitly evaluate these associations.

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Abbreviations

CBCL	Child Behavior Checklist
PME	prenatal methamphetamine exposure

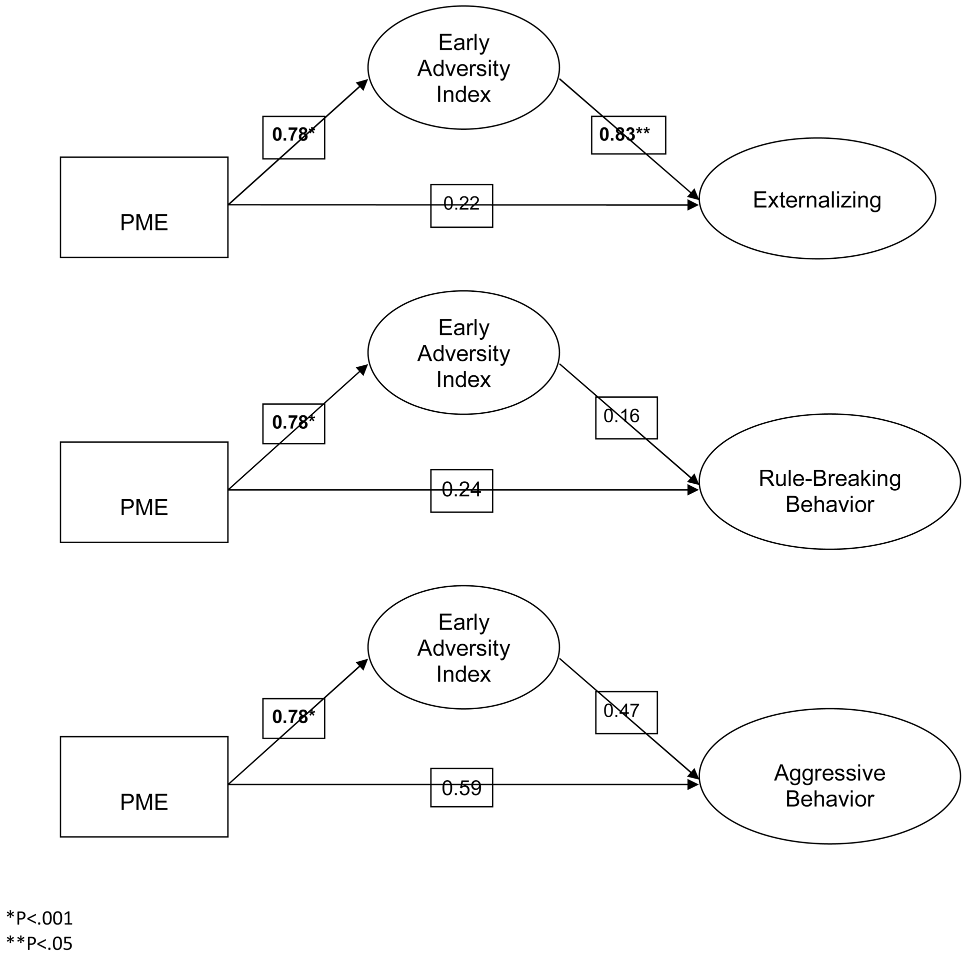

Figure 1.
Relationship between early adversity and behavioral problems adjusted for prenatal exposure to alcohol, marijuana, tobacco, gender, and study site.

Table 1

Comparison of dyads included and not included at 7.5 year evaluation.

N (%) or Mean (SD)	Included (n = 290)	Not Included (n= 122)	P-Value
Race			0.644
White	117 (40.3%)	43 (35.2%)	
Hispanic	59 (20.3%)	33 (27.0%)	
Pacific Islander	51 (17.6%)	20 (16.4%)	
Asian	41 (14.1%)	16 (13.1%)	
Black	14 (4.8%)	8 (6.6%)	
American Indian	8 (2.8%)	2 (1.6%)	
Low SES (Hollingshead Index=5)	64 (22.1%)	29 (24.2%)	0.644
Partner at birth	162 (55.9%)	65 (53.3%)	0.630
Education <12 years	120 (41.5%)	52 (43.0%)	0.786
Maternal Age	24.9 (5.5)	25.8 (5.9)	0.167
Prenatal MA use	146 (50.3%)	58 (47.5%)	0.603
Heavy prenatal MA use (>=3 days/week)	27 (9.4%)	8 (6.8%)	0.619
Prenatal tobacco use	156 (53.8%)	62 (50.8%)	0.581
Prenatal alcohol use	69 (23.8%)	37 (30.3%)	0.166
Prenatal marijuana use	51 (17.6%)	25 (20.5%)	0.488
Male	153 (52.8%)	67 (54.9%)	0.688
Gestational age	38.6 (2.2)	38.7 (1.8)	0.689
Birth weight	3234 (602)	3279 (593)	0.488
Birth length	50.4 (3.5)	50.4 (3.1)	0.966
Birth head circumference	33.8 (1.8)	34.2 (1.9)	0.038

Table 2

Maternal and neonatal characteristics by methamphetamine exposure

N (%)or Mean (SD)	Exposed (n = 146)	Comparison (n= 144)	P-Value
Maternal Characteristics			
Race			
White	56 (38.4%)	61 (42.4%)	0.924
Hispanic	30 (20.5%)	29 (20.1%)	
Pacific Islander	27 (18.5%)	24 (16.7%)	
Asian	22 (15.1%)	19 (13.2%)	
Black	6 (4.1%)	8 (5.6%)	
American Indian	5 (3.4%)	3 (2.1%)	
Low SES (Hollingshead Index=5)	50 (34.2%)	14 (9.7%)	<0.001
Partner at birth	64 (43.8%)	98 (68.1%)	<0.001
Education <12 years	67 (45.9%)	53 (37.1%)	0.128
Maternal age	25.5 (5.6)	24.4 (5.3)	0.092
Prenatal tobacco use	120 (82.2%)	36 (25.0%)	<0.001
Prenatal alcohol use	49 (33.6%)	20 (13.9%)	<0.001
Prenatal marijuana use	45 (30.8%)	6 (4.2%)	<0.001
Neonatal Characteristics			
Male	77 (52.7%)	76 (52.8%)	0.995
Birth weight (g)	3171 (634)	3298 (563)	0.071
Birth length (cm)	49.7 (3.7)	51.1 (3.1)	0.001
Birth head circumference (cm)	33.6 (1.8)	33.9 (1.8)	0.130
Gestational Age (weeks)	38.2 (2.4)	39.1 (1.8)	0.001

Note: Exposed and Comparison groups were group matched on race, maternal education status, and infant birth weight

Table 3

Overall Early Adversity Index by exposure group.

N (%) or Mean (SD)	PME	Comparison	Overall
Overall Early Adversity Index **	2.95 (1.47)	1.97 (1.27)	2.46 (1.45)
Maternal Postnatal Substance Use (n = 281)	114 (80%)	101 (73%)	215 (77%)
Any Extreme Poverty (n = 290)*	56 (38%)	36 (25%)	92 (32%)
Any Primary Caregiver Changes (n = 289) **	75 (52%)	9 (6%)	84 (29%)
Any Reported Caregiver Sexual or Physical Abuse (n = 256)	7 (6%)	5 (4%)	12 (4%)
Any Positive Maternal Diagnosis of Psychological Distress (n = 290)	82 (56%)	66 (46%)	148 (51%)
Any High Maternal Depression (n = 290)	25 (17%)	14 (10%)	39 (13%)
Poor Quality Living Environment (n = 251)	23 (19%)	19 (15%)	42 (17%)
High Community Violence (n = 290)	22 (15%)	25 (17%)	47 (16%)
Any Low Social Position (n = 290)**	26 (18%)	8 (6%)	34 (12%)

*Difference between PME and comparisons, $p < 0.05$

**Difference between PME and comparisons, $p < 0.001$

Table 4

CBCL scores by exposure group.

Mean (SD)	PME	Comparison	Overall
Externalizing*	56.8 (10.9)	54.2 (9.4)	55.5 (10.3)
Rule-Breaking Behavior*	2.9 (2.6)	2.2 (2.0)	2.6 (2.3)
Aggressive Behavior*	8.4 (6.8)	6.6 (5.2)	7.5 (6.1)
Internalizing	51.6 (9.6)	50.1 (9.5)	50.9 (9.6)
Anxious/Depressed	3.3 (2.7)	3.0 (2.8)	3.1 (2.8)
Withdrawn	1.5 (1.8)	1.2 (1.6)	1.4 (1.7)
Somatic Complaints	1.3 (1.7)	1.2 (1.6)	1.3 (1.6)
Total Problems	54.8 (10.6)	53.3 (9.3)	54.1 (10.0)

*Difference between PME and comparisons, $p < 0.05$