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Prenatal Methamphetamine Exposure and Childhood Behavior Problems at 3 and 5 Years of Age

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WHAT'S KNOWN ON THIS SUBJECT: Prenatal methamphetamine exposure has been related to deficits in fetal growth, changes in infant neurobehavior, and fine motor deficits, but little is known about its developmental effects on behavior problems in early childhood.

WHAT THIS STUDY ADDS: This is the first prospective study to identify behavior problems associated with prenatal methamphetamine exposure. Mood difficulties and acting-out behavior are increased in exposed children by age 3 years. Early identification and intervention may prevent escalation into delinquency and psychopathology.

abstract

OBJECTIVE: We evaluated behavior problems in children who were prenatally exposed to methamphetamine (MA) at ages 3 and 5 years.

METHODS: The Infant Development, Environment, and Lifestyle study, a prospective, longitudinal study of prenatal MA exposure and child outcome, enrolled subjects postpartum in Los Angeles, California; Honolulu, Hawaii; Des Moines, Iowa; and Tulsa, Oklahoma. Prenatal exposure was determined by maternal self-report and/or meconium results. Exposed and comparison groups were matched on race, birth weight, public health insurance, and education. Mothers in the comparison group denied use and had a negative meconium screen for amphetamines. Prenatal exposures to tobacco, alcohol, or marijuana occurred in both groups. At ages 3 and 5 years, 330 children (166 exposed and 164 comparison) were assessed for behavior problems by using the caregiver report on the Child Behavior Checklist. General linear mixed models were used to determine the effects of prenatal MA exposure, including heavy exposure (≥3 days per week), age, and the interaction of exposure and age on behavior problems with adjustment for other drugs of abuse and environmental risk factors.

RESULTS: MA exposure was associated with increased emotional reactivity and anxious/depressed problems at both ages and externalizing and attention-deficit/hyperactivity disorder problems by age 5 years. Heavy exposure was related to attention problems and withdrawn behavior at both ages. There were no effects of MA on the internalizing or total behavior problems scales.

CONCLUSIONS: This first report of behavior problems in patients as young as 3 years associated with MA exposure identifies an important public health problem. Continued follow-up can inform the development of preventive intervention programs. *Pediatrics* 2012;129:681–688

Methamphetamine (MA) use is a worldwide problem, with more users than cocaine and opiates combined.[1] In the United States, MA use is mostly in the western and Midwestern states, with a recent surge in the south.[2] Unlike with other drugs of abuse, more women than men are first-time users and comprise one-half of those seeking treatment of MA use, raising concern for the impact of prenatal MA use on children. In 2009, 6.7% of those seeking treatment of MA abuse in the United States were pregnant women.[3]

Research on the impact of prenatal MA exposure on child development is emerging from the only large, prospective longitudinal study of prenatal MA use, the Infant Development, Environment, and Lifestyle (IDEAL) study.[4] Previous MA findings from IDEAL include increased small for gestational size at birth[5] and decreased length through 3 years,[6] poor quality of movement, low arousal, and increased stress signs in the newborn period[7] and poor grasping ability at 1 and 3 years of age.[8] The only comparable study conducted in Sweden showed increased drowsiness during the newborn period[9] and increased behavior problems in amphetamine-exposed children.[10] However, this study had methodologic concerns, including small sample size, no control group, and confounds with other drugs.

Research on prenatal cocaine exposure is instructive because both cocaine and MA are sympathomimetic agents. However, MA's neurotoxic effects may be greater due to its longer half-life and multiple mechanisms of action.[11] Similar to cocaine, MA blocks the reuptake of dopamine and other catecholamines,[12] but MA also increases the release of dopamine and norepinephrine.[13] As with cocaine, MA has vasoconstrictive effects, resulting in decreased uteroplacental blood flow and fetal hypoxia.[14,15] Similar to MA, early findings related to cocaine exposure include

newborn growth deficits[16] and low arousal and stress signs.[17] Reported motor deficits in motor functioning were resolved by 18 months.[18]

In studies of behavioral problems using the Child Behavior Checklist (CBCL),[19] cocaine exposure has been associated with externalizing and or internalizing behavior problems in children as young 3 years[20,21] through school age,[20,22,23] with specific behavioral syndromes of attention problems at ages 4,[24] 6,[22] and 9 to 11[25] years, aggressive behavior at 3[21] and 7[22] years, anxiety/depression at 3[21] and 8[23] years, and withdrawn behavior at 3 years.[21]

To the best of my knowledge, we present the first longitudinal study of behavioral problems associated with prenatal MA exposure adjusted for prenatal exposure to other drugs and environmental risk.[20,24,26] Similar to studies of cocaine exposure, the CBCL was first administered at 3 years of age, then at 5 years. Our findings may be particularly important to identify early behavior problems before school entry.

METHODS

Between 2002 and 2004, IDEAL subjects were recruited postpartum at 4 data-collection sites: Los Angeles, California; Honolulu, Hawaii; Des Moines, Iowa; and Tulsa, Oklahoma. Detailed recruitment methods for the IDEAL study have been reported previously.[4,27] This study was approved by the institutional review boards at each site, and written informed consent was obtained from all subjects. A National Institute on Drug Abuse Certificate of Confidentiality was obtained that assured confidentiality of information regarding the mothers' drug use.

At recruitment, mothers were interviewed for sociodemographic and prenatal substance use information. Meconium was collected from each infant and analyzed at a central laboratory (US Drug Testing Laboratories,

Inc., Des Plaines, IA) for drug metabolites.[28] MA exposure was determined by self-reported MA use during this pregnancy and/or a positive meconium screen and gas chromatography/mass spectroscopy confirmation. A matched case-control study design was used. The exposed ($n = 204$) and comparison ($n = 208$) groups were recruited consecutively from the same sites and matched on maternal race, birth weight category (<1500, 1500–2500, and >2500 g), insurance (private/public), and education (high school completed/not completed). Inclusion in the comparison group required denial of MA use during this pregnancy and a negative meconium screen for MA. Comparison dyads with characteristics that were difficult to match (eg, Asian race, >2500 g birth weight, public insurance, high school not completed) were enrolled before a matching exposed dyad, leading to slightly different sample sizes in the 2 groups. Prenatal exposure to alcohol, tobacco, and marijuana was included in both groups as background variables.

The sample for this study included all children who were evaluated for behavioral problems at ages 3 or 5 years. The follow-up rate was 70% at 3 years and 76% at 5 years (2 cases at 3 years and 7 cases at 5 years had missing CBCL information). There were 330 subjects (262 at both ages, 26 at 3 years only, and 42 at 5 years only) or 80% of the cohort (166 exposed and 164 comparison). Comparison of the characteristics of the 330 subjects in this study with the 82 not included (Table 1) revealed no significant differences on all characteristics, except mothers who were not included used more marijuana during pregnancy.

The CBCL[19] 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

TABLE 1 Comparison of Dyads Included and Not Included in the Study

Characteristics	Included (n = 330)	Not Included (n = 82)	P
Maternal/demographic			
Race			.967
White	127 (38.4)	33 (40.2)	
Hispanic	74 (22.4)	18 (22.0)	
Pacific Islander	58 (17.6)	13 (15.9)	
Asian	45 (13.6)	12 (14.6)	
Black	17 (5.2)	5 (6.1)	
American Indian	9 (2.7)	1 (1.2)	
Low SES (Hollingshead V)	72 (21.8)	21 (25.6)	.457
Public insurance	292 (88.5)	77 (93.9)	.507
No partner	147 (44.6)	38 (46.3)	.805
Education <12 y	137 (41.5)	35 (42.7)	.803
Maternal age, y	25.2 ± 5.7	25.1 ± 5.2	.945
Prenatal MA use	166 (50.3)	38 (46.3)	.539
MA heavy use (≥3 d/wk across pregnancy)	29 (8.8)	6 (7.3)	.588
Prenatal alcohol use	82 (24.9)	24 (29.3)	.401
Absolute alcohol/day (oz) across pregnancy	0.06 ± 0.37	0.08 ± 0.24	.757
Prenatal marijuana use	60 (18.2)	16 (19.5)	.753
Joints/day across pregnancy	0.04 ± 0.18	0.26 ± 1.7	.023
Prenatal tobacco exposure	179 (54.2)	39 (47.6)	.323
Cigarettes/d across pregnancy	4.2 ± 7.1	4.5 ± 7.2	.788
Neonatal			
Male gender	170 (51.5)	50 (61.0)	.139
Birth weight, g	3231 ± 606	3312 ± 570	.276
Gestational age, wk	38.6 ± 2.1	39.0 ± 1.7	.140
Low birth weight	41 (12.4)	6 (7.3)	.245
Length, cm	50.3 ± 3.5	50.6 ± 2.9	.477
Head circumference, cm	33.8 ± 1.8	34.2 ± 1.7	.134

Data are presented as n (%) or mean ± SD.

co-occurring problems and are the basis for internalizing (emotionally reactive, anxious/depressed, somatic complaints, or withdrawn) and externalizing (attention problems and aggressive behavior) scores. Higher scores indicate more problems. Some items on the CBCL are consistent with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnostic categories. We include the DSM-oriented score of attention deficit based on evidence of its clinical significance.[29]

Most caregivers who completed the CBCL at 3 and 5 years were biological parents (78% and 74%, respectively). Other caregivers were foster or adoptive parents (12% and 17%), relatives (9% and 5%), or nonrelatives (2% and 4%). The caregiver was the same at both ages in 84% of the cases. No significant differences in CBCL scores by caregiver were found (P values from .139 to .962).

At recruitment, demographic and neonatal characteristics were obtained from the lifestyle interview including race, gender, insurance (public/private), maternal age, single status/no partner involvement (yes or no), socioeconomic status (SES), birth weight, and gestational age. Birth length and head circumference were obtained from the infant's medical chart. SES was calculated by using the 4-factor Hollingshead Index adapted for single parent and nonnuclear families,[30,31] with Hollingshead level V indicating low SES.

Postnatal caregiver and environmental characteristics were measured on multiple visits. Measures from the lifestyle interview at 1 month and 1, 2, 3, and 5 years included physical and sexual abuse based on report to Child Protective Services (yes/no) and any change in primary caregiver (none, 207; one, 62; two, 38; three, 1; and four, 4). The Brief Symptom Inventory, administered at 1

month and 1 and 3 years, provided an overall score of caregiver psychological symptoms.[32] The quality of the home environment, computed as an overall summary score, was measured at 2.5 years of age by using the Home Observation for Measurement of the Environment Early Childhood inventory.[33] The personal safety section of the Substance Use Inventory at 3 years assessed domestic violence experienced by the caregiver (yes/no).

Prenatal use of MA and other drugs of abuse including quantity and frequency of use was obtained from the Substance Use Inventory,[34] from which level of use was determined. Consistent with other IDEAL studies,[7,8] heavy MA exposure was defined as maternal use ≥3 days per week across pregnancy. Some use was any MA use <3 days per week across pregnancy. The pattern of use according to trimester (Table 2) indicated overall decline and quitting MA use over the course of the pregnancy. However, declining and quitting MA use occurred sooner in the some use versus heavy use group (first to second trimester, P = .001 in both cases). Eighteen heavy users (62%) used in all 3 trimesters versus 21 (16%) some users (P < .001).

Level of exposure to other drugs of abuse was calculated as cigarettes per day, ounces of absolute alcohol per day, and joints per day for marijuana across pregnancy.[35,36] Postnatal use of MA, alcohol, tobacco, and marijuana (yes/no for each drug) was similarly measured at 1, 2, 3, and 5 years.

General linear models were used to compare means for continuous variables and χ^2 tests for categorical variables (Tables 1–3). General linear mixed models (SAS PROC MIXED, version 9.1.3) tested the effects of MA exposure (any exposure; level of MA exposure) and longitudinal CBCL measures at ages 3 and 5 years and the interaction of MA exposure and age, adjusted for

TABLE 2 Frequency of Self-Reported MA Use According to Trimester of Pregnancy

MA Use	Heavy MA Use ($n = 29$)			Some MA Use ($n = 132$)		
	First Trimester	Second Trimester	Third Trimester	First Trimester	Second Trimester	Third Trimester
Daily	17 (58.6)	13 (44.8)	4 (13.8)	12 (9.1)	1 (0.8)	1 (0.8)
3–6 d/wk	11 (37.9)	14 (48.3)	10 (34.5)	36 (27.3)	9 (6.8)	1 (0.8)
1–2 d/wk	0 (0)	2 (6.9)	2 (6.9)	23 (17.4)	14 (10.6)	8 (6.1)
1–3 d/mo	0 (0)	0 (0)	1 (3.4)	14 (10.6)	17 (12.9)	12 (9.1)
1–2 d/3 mo	0 (0)	0 (0)	1 (3.4)	18 (13.6)	19 (14.4)	26 (19.7)
Not at all	1 (3.4)[a]	0 (0)	10 (34.5)	27 (20.5)	71 (53.8)	83 (62.9)
Days/wk	5.91 ±1.69	5.14 ± 1.90	2.77 ± 2.70	2.05± 2.22	0.53 ± 1.10	0.23 ± 0.76

Five of the 161 MA users in this study were identified as exposed according to toxicology results only. Data are presented as n (%) or mean ± SD.

[a] One case was classified as a heavy user who abstained in the first trimester: second trimester use, 3.5 days per week; third trimester use, 5.5 days per week.

covariates (Tables 4 and 5). Level-of-use models included separate tests for heavy and some MA exposure versus the comparison group. Interactions of covariates and MA exposure or level of MA exposure were examined but did not meet criteria for inclusion ($P > .05$). There were 16% and 13% missing values for the Home Observation for Measurement of the Environment scale and domestic violence, respectively. We therefore applied multiple imputation[37,38] by using SAS PROC MI and MIAnalyze. The results were very similar to analysis without imputation. The final model from the imputed dataset was used to retain the largest sample size.

A priori covariates included prenatal exposure to alcohol, tobacco, and marijuana; gender; SES; and birth weight. Any exposure to alcohol, tobacco, or marijuana exposure was included in analyses of any MA exposure, with level of exposure included in analyses of heavy MA exposure. Other variables were examined for inclusion as covariates on the basis of published literature and characteristics that differed between exposure groups ($P < .05$) if not highly correlated with other covariates ($r = 0.70$). Covariates measured at multiple time points were averaged (eg, caregiver psychological symptoms) or aggregated over time (eg, any postnatal tobacco use at 1–5 years) to provide the best estimate of the child-rearing environment to date. Covariates were included if associated with any of the outcomes ($P < .15$). All models were adjusted for prenatal tobacco, alcohol, and marijuana exposures; birth weight; gender; low SES; maternal age; no partner; primary caregiver change; domestic violence; postnatal caregiver use of MA; alcohol, tobacco, and marijuana exposure; caregiver psychological symptoms; quality of the home; and reported child abuse. Continuous covariates (eg, maternal age)

TABLE 3 Sample Characteristics According to MA Exposure

Characteristics	Exposed ($n = 166$)	Comparison ($n = 164$)	P
Maternal and demographic characteristics at birth			
Race			.876
White	62 (37.4)	65 (39.6)	
Hispanic	39 (23.5)	35 (21.3)	
Pacific Islander	30 (18.1)	28 (17.1)	
Asian	22 (13.3)	23 (14.0)	
Black	7 (4.2)	10 (6.1)	
American Indian	6 (3.6)	3 (1.8)	
Low SES (Hollingshead V)	56 (33.7)	16 (9.8)	<.0001
Public insurance	151 (91.0)	141 (86.0)	.018
No partner	94 (56.6)	53 (32.3)	<.0001
Education <12 y	76 (45.8)	61 (37.2)	.124
Maternal age, y	25.6 ± 5.7	24.7 ± 5.7	.157
Prenatal alcohol use	59 (35.5)	23 (14.0)	<.001
Absolute alcohol/d (oz) across pregnancy	0.12 ± 0.52	<0.01 ± 0.02	.005
Prenatal marijuana use	53 (31.9)	7 (4.3)	<.001
Joints/d across pregnancy	0.07 ± 0.23	0.01 ± 0.10	.003
Prenatal tobacco use	134 (80.7)	45 (27.4)	<.001
Cigarettes/d across pregnancy	6.8 ± 8.2	1.6 ± 4.6	<.001
Neonatal characteristics			
Male gender	87 (52.4)	83 (50.6)	.744
Birth weight, g	3178 ± 628	3285 ± 579	.110
Gestational age, wk	38.2 ± 2.4	39.0 ± 1.8	.001
Low birth weight	21 (12.7)	20 (12.2)	.999
Length, cm	49.7 ± 3.7	51.0 ± 3.1	.001
Head circumference, cm	33.6 ± 1.8	34.0 ± 1.9	.054
Postnatal characteristics			
Caregiver change (by 5 y)	98 (59.0)	16 (9.8)	<.001
Any postnatal MA use (by 5 y)	38 (22.9)	5 (3.0)	<.001
Any postnatal tobacco use (by 5 y)	100 (60.2)	76 (46.3)	.011
Any postnatal alcohol use (by 5 y)	107 (64.5)	116 (70.7)	.217
Any postnatal marijuana use (by 5 y)	27 (16.3)	11 (6.7)	.009
Domestic violence (3 y)	7 (4.2)	6 (3.7)	.783
Average caregiver psychological symptoms (1 mo and 2 and 3 y)	0.47 ± 0.41	0.47 ± 0.42	.625
Quality of home (2.5 y)	34.0 ± 4.1	34.2 ± 3.9	.698
Reported child abuse (by 5 y)	12 (7.2)	5 (3.0)	.133

Data are presented as n (%) or mean ± SD.

TABLE 4 Behavior Problems Scores According to Prenatal MA Exposure

Outcome	MA Exposure Group				Adjusted [a]					
	Age 3 Years		Age 5 Years		Exposure[b]		Age[b]		Interaction[c]	
	Exposed (n = 141)	Comparison (n = 147)	Exposed (n = 153)	Comparison (n = 151)	β (SE)	P	β (SE)	P	β (SE)	P
Externalizing	53.0 ± 1.9	52.0 ± 2.2	53.1 ± 2.0	49.6 ± 2.3	2.8 (2.0)	.150	−2.4 (0.8)	.003	2.5 (1.2)	.034
Attention problems	2.6 ± 0.4	2.6 ± 0.4	2.8 ± 0.4	2.7 ± 0.4	0.40 (0.4)	.278	0.01 (0.2)	.995	0.15 (0.2)	.552
Aggressive behavior	12.9 ± 1.3	11.8 ± 1.6	12.6 ± 1.4	10.0 ± 1.6	2.1 (1.4)	.123	−1.9 (0.6)	.002	1.5 (0.8)	.068
ADHD issues	5.3 ± 0.6	5.2 ± 0.6	5.5 ± 0.6	4.6 ± 0.6	0.62 (0.6)	.259	−0.61 (0.2)	.013	0.78 (0.4)	.029
Internalizing	50.9 ± 1.8	48.7 ± 2.2	54.2 ± 1.9	50.8 ± 2.2	3.5 (1.9)	.057	2.1 (0.8)	.007	1.1 (1.2)	.350
Emotionally reactive	3.2 ± 0.5	2.3 ± 0.6	3.7 ± 0.5	2.5 ± 0.6	1.4 (0.5)	.006	0.22 (0.2)	.318	0.29 (0.3)	.363
Anxious/depressed	2.8 ± 0.4	2.0 ± 0.5	3.4 ± 0.4	2.3 ± 0.5	1.0 (0.4)	.019	0.35 (0.2)	.010	0.28 (0.3)	.359
Somatic complaints	1.8 ± 0.3	1.8 ± 0.4	2.3 ± 0.4	2.3 ± 0.4	−0.06 (0.3)	.861	0.53 (0.2)	.002	−0.04 (0.2)	.883
Withdrawn	1.5 ± 0.4	1.4 ± 0.5	1.9 ± 0.4	1.7 ± 0.5	0.44 (0.4)	.273	0.37 (0.2)	.033	0.040 (0.2)	.866
Total problems	52.2 ± 1.8	51.1 ± 2.1	52.9 ± 1.8	50.2 ± 2.1	2.9 (1.8)	.119	−0.91 (0.8)	.227	1.63 (1.1)	.134

Data are presented as adjusted mean ± SE unless otherwise noted.

[a] Adjusted analyses tested main effects of MA exposure and child age at assessment (3 vs 5 years) and the interaction of exposure and age, adjusted for prenatal exposure to alcohol, tobacco, and marijuana; birth weight; gender; SES; maternal age; single (no partner); caregiver change; domestic violence; postnatal use of MA; tobacco, alcohol, and marijuana exposure; caregiver psychological symptoms; the quality of the home; child abuse; and study site.

[b] The reference group was the comparison group for analysis of exposure and 3 years for analysis of age.

[c] A least squares mean procedure was applied to follow up a significant interaction.

were grand mean centered to increase precision and interpretation of the intercept. Subjects were nested in site to account for the correlations among the subjects from the same site and to provide more accurate estimates.[39]

RESULTS

Relative to the comparison group, the MA-exposed group was more likely to have lower SES, public insurance, be without a partner, and use alcohol, tobacco, and marijuana during pregnancy (Table 3). MA-exposed infants were on average 5 days younger in gestational age and 1.3 cm shorter at birth than infants in the comparison group. Postnatally, there was increased likelihood of a caregiver change and use of MA, tobacco, and marijuana in the exposed group than in the comparison group.

Longitudinal analyses (Table 4) adjusted for covariates showed 2 main effects for MA exposure. Across both ages as rated by the caregiver, the exposed group was more emotionally reactive and anxious/depressed than the comparison group.

There were 2 interactions between MA exposure and age. For externalizing behavior, there was no exposure effect at 3 years (P = .523), but at 5 years, the exposed group had higher scores than the comparison group (P = .022). For attention-deficit/hyperactivity disorder (ADHD) issues, there was no exposure effect at 3 years (P = .820), but at 5 years, the exposed group had higher scores than the comparison group (P = .040).

There were 5 main effects for age excluding outcomes with interactions. Relative to 3 years, children at 5 years showed less aggressive behavior and higher scores on internalizing, anxious/depressed, somatic complaints, and withdrawn scales.

Analyses of the level of exposure (Table 5) revealed 3 main effects across age. The scores for attention problems and being withdrawn were higher in the heavy exposure versus the comparison group. The score for emotionally reactive was higher in the some exposure versus the comparison group. The main effects for age were the same as in the previous analyses (Table 4) (data not shown).

There were 3 interactions of some exposure and age that showed the same pattern at each age. For externalizing behavior, there were no effect of some exposure at 3 years (P = .818), but at 5 years, the some exposed group had higher scores than the comparison group (P = .013). For aggressive behavior, there was no exposure effect of some exposure at 3 years (P = .520), but at 5 years, the some exposed group had higher scores than the comparison group (P = .008). For ADHD issues, there was no effect of some exposure at 3 years (P = .694), but at 5 years, the some exposed group had higher scores than the comparison group (P = .041).

The only significant psychosocial predictor for all behavior problems was caregiver psychological symptoms (P = .010 to < .001). Boys had more externalizing problems (P < .001), attention problems (P < .001), aggressive behavior (P = .001), ADHD (P < .001), internalizing (P = .043), emotional reactivity (P = .022), withdrawal (P = .021), and total problems (P = .002) than girls. Children of younger mothers had more internalizing behavior (P = .012), total (P = .027), attention (P = .008), ADHD (P = .036), and anxious/depressed (P < .012) problems. Poorer quality of the home was related to more attention problems (P = .030) and aggressive behavior (P = .043).

TABLE 5 CBCL According to Level of MA Exposure

Outcome	Level of Prenatal MA Exposure						Adjusted [a]							
	Age 3 Years			Age 5 Years			Heavy [b]		Interaction [c]		Some [b]		Interaction [c]	
	Heavy (n = 26)	Some (n = 112)	Comparison (n = 147)	Heavy (n = 29)	Some (n = 119)	Comparison (n = 151)	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
Externalizing	56.8 ± 2.7	53.3 ± 1.9	52.9 ± 2.2	54.9 ± 2.8	54.1 ± 2.0	50.5 ± 2.2	5.9 (3.8)	.12	0.56 (2.1)	.794	1.8 (1.9)	.346	3.3 (1.3)	.010
Attention problems	3.9 ± 0.5	2.8 ± 0.4	2.6 ± 0.4	3.4 ± 0.5	2.8 ± 0.4	2.6 ± 0.4	2.2 (0.7)	.002	−0.56 (0.4)	.205	0.11 (0.4)	.765	0.32 (0.3)	.223
Aggressive behavior	14.9 ± 1.9	13.2 ± 1.4	12.5 ± 1.5	13.4 ± 1.9	13.3 ± 1.4	10.7 ± 1.5	3.4 (2.6)	.196	0.37 (1.5)	.804	1.4 (1.3)	.273	2.0 (0.9)	.025
ADHD issues	6.7 ± 0.8	5.4 ± 0.6	5.6 ± 0.6	6.2 ± 0.8	5.8 ± 0.6	5.0 ± 0.6	1.8 (1.1)	.083	0.12 (0.6)	.846	0.20 (0.5)	.711	1.0 (0.4)	.008
Internalizing	52.7 ± 2.6	50.9 ± 1.8	48.8 ± 2.1	55.8 ± 2.6	54.3 ± 1.9	51.0 ± 2.1	7.0 (3.6)	.052	1.0 (2.0)	.620	3.0 (1.8)	.092	1.3 (1.2)	.304
Emotionally reactive	3.0 ± 0.7	3.1 ± 0.5	2.4 ± 0.6	3.5 ± 0.7	3.7 ± 0.5	2.6 ± 0.6	1.2 (1.0)	.191	0.27 (0.6)	.643	1.1 (0.5)	.017	0.39 (0.3)	.258
Anxious/depressed	2.6 ± 0.6	2.7 ± 0.4	2.1 ± 0.5	3.9 ± 0.6	3.2 ± 0.5	2.4 ± 0.5	1.0 (0.9)	.234	0.92 (0.5)	.092	0.80 (0.4)	.060	0.18 (0.3)	.584
Somatic complaints	2.0 ± 0.5	1.7 ± 0.3	1.6 ± 0.4	2.3 ± 0.5	2.2 ± 0.4	2.1 ± 0.4	0.71 (0.6)	.279	−0.30 (0.4)	.504	0.03 (0.3)	.925	0.01 (0.3)	.994
Withdrawn	2.2 ± 0.6	1.6 ± 0.4	1.5 ± 0.4	2.2 ± 0.6	2.2 ± 0.4	1.9 ± 0.4	1.6 (0.8)	.041	−0.36 (0.4)	.416	0.40 (0.4)	.287	0.14 (0.3)	.601
Total problems	54.7 ± 2.5	52.3 ± 1.8	51.6 ± 2.0	54.6 ± 2.6	53.4 ± 1.9	50.7 ± 2.3	6.2 (3.6)	.084	0.87 (1.9)	.655	2.0 (1.8)	.256	2.0 (1.2)	.077

Main effects for age are shown in Table 4 and are not repeated in this table. Data are presented as adjusted mean ± SE unless otherwise noted.

[a] Adjusted analyses tested main effects of MA exposure and child age at assessment (3 vs 5 years) and the interaction of exposure and age, adjusted for prenatal exposure to ounces of absolute alcohol per day; number of cigarettes per day; joints per day; birth weight; gender; SES; maternal age; single (no partner); caregiver change; domestic violence; postnatal use of MA: tobacco, alcohol, and marijuana exposure; caregiver psychological symptoms; the quality of the home; child abuse; and study site.

[b] The reference group was the comparison group for analysis of heavy and some MA exposure.

[c] A least squares mean procedure was applied to follow up a significant interaction.

Postnatal tobacco use was associated with increased total problems (P = .038) and withdrawal (P = .020). Inconsistent with other studies,[20,24,36] prenatal alcohol exposure predicted decreased attention and ADHD issues (P = .016 and .003, respectively), prenatal marijuana exposure predicted decreased anxious/depressed problems (P = .039), and postnatal alcohol use predicted decreased withdrawal (P = .006).

All models revealed significant effects for site (all, P < .001), indicating the correlation of subjects within site.

DISCUSSION

This is the first controlled study of behavior problems in children with prenatal MA exposure, and with measurement at 2 ages, we found developmental changes in behavior problems. We found more externalizing and ADHD problems related to MA exposure at 5 years but not at 3 years. These exposure effects were due to decreased externalizing behavior and ADHD problems in the comparison group at 5 years, with no change in the MA-exposed group. There was also a decrease in aggressive behavior from 3 to 5 years, unrelated to MA exposure.

Unlike externalizing behaviors, internalizing behavior and the syndrome scores for withdrawn behavior and somatic complaints increased across 3 to 5 years, unrelated to MA exposure, which is consistent with normative developmental trajectories.[40] However, at both ages, the MA exposure group had higher scores than the comparison group on emotional reactivity and anxious/depressed problems. The process of behavior control during preschool-aged years may be attenuated in MA-exposed children while the tendency toward increased negative internal states is maintained. These developmental trajectories may suggest unique endophenotypes related to prenatal MA exposure.

Our analysis of heavy MA exposure revealed more attention problems and withdrawn behavior with heavy use than in the comparison group that were not observed with the overall exposed group. Inspection of the means and the relative small group size of heavy exposure ($n = 26$) suggest that findings of some use but not heavy use may reflect greater power in the some group rather a substantively greater set of deficits for less MA use than more.

Given that the attention problems and ADHD scales are conceptually related and shared 3 items, we anticipated overlap in findings, but this was not the case. Attention problems increased across 3 and 5 years whereas ADHD issues increased only at 5 years. Thus, there may be early indicators of poor attention at 3 years but specific indicators of ADHD in MA-exposed children at 5 years.

Our findings on externalizing and component behaviors are consistent with studies of children with prenatal cocaine exposure.[20,21,24] although our analysis of age provides new information that increased externalizing related to MA exposure was not observed at 3 years of age. Given the common mechanisms of action of MA and cocaine, the similarity in findings may not seem surprising. However, the demographic characteristics of women who use MA versus cocaine during pregnancy are quite different. Most of the prenatal cocaine exposure studies have been conducted with inner-city, black, impoverished, poorly educated mothers. By contrast, the IDEAL sample is mostly white, Hispanic and Asian, working class, educated, and not from inner-city areas. In fact, many are from rural areas. Despite adjustment for demographic factors, the population differences suggest that these effects on behavior problems are quite robust and may have substantial public health implications because problems as noted on the CBCL tend to persist over time[41] and predict later psychopathology and criminal behavior that place tremendous burdens on society.[42] The ability to identify specific behavioral syndromes in children as early as preschool age could lead to the development of preventive intervention programs.

Our findings of postnatal effects for tobacco could be due to exposure to second-hand smoke and/or caregiving factors. As with other researchers, we found that drugs included as covariates can show few or no effects[43] or contradictory effects,[21,25] which may occur from low incidence of the drug or correlation with MA use or other variables in the multivariate models. Pervasive behavior problems in boys were found across externalizing and all related syndrome scores and internalizing problems, including emotionally reactivity and withdrawn behavior. These gender effects have not been reported at this age in studies of prenatal cocaine exposure.[20,21] Our findings are consistent with others that have found behavior problems related to caregiver psychological symptoms[20,24] and poor-quality homes related to increased attention problems, aggression, and ADHD problems.[26,44]

As the only cohort study of its kind, 1 limitation of the study is that our findings may not generalize to all populations of women who use MA during pregnancy. Furthermore, the sample was recruited at delivery, which may potentially affect recall of early pregnancy drug use. Because CBCL findings are based on caregiver report, there could be reporting bias. We chose not to analyze trimester effects in addition to reported analyses due to the pattern of declining use and quitting during the second and third trimester. Finally, our measure of child abuse through caregiver report of Child Protective Services involvement likely underestimates abuse. Despite these limitations, the IDEAL study provides our first look at the emergence of behavior problems in young children with prenatal MA exposure and addresses an important public health problem.

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