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The Effects of Prenatal Methamphetamine Exposure on Childhood Growth Patterns from Birth to 3 Years of Age

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Abstract

We examined the effects of prenatal methamphetamine (MA) exposure on growth parameters from birth to age 3 years. The 412 subjects included ($n = 204$ exposed) were enrolled at birth in the Infant Development, Environment and Lifestyle study, a longitudinal study assessing the effects of prenatal MA exposure on childhood outcomes. Individual models were used to examine the effects of prenatal MA exposure on weight, head circumference, height, and weight-for-length growth trajectories. After adjusting for covariates, height trajectory was lower in the exposed versus the comparison children ($p = 0.021$) over the first 3 years of life. Both groups increased height on average by 2.27 cm per month by age 3 years. In term subjects, MA exposure was also associated with a lower height trajectory ($p = 0.034$), with both the exposed and comparison groups gaining 2.25 cm per month by age 3 years. There was no difference in weight, head circumference, or weight-for-length growth trajectories between the comparison and the exposed groups. Children exposed prenatally to MA have a modest decrease in height growth trajectory during the first 3 years of life with no observed difference in weight, head circumference, or weight-for-length trajectories.

Keywords

height; antenatal; drug; amphetamine

Methamphetamine (MA) use continues to be a significant problem in the United States. The number of adults age 12 and over who have tried MA once in their lifetime increased to 5.3% in 2002 from 4.3% in 1999 and 2.5% in 1997.^{1–3} By 2007, the National Survey on Drug Use and Health report estimated that 1.3 million people over the age of 12 years have

used MA in the past year and ~14.2 million people have tried MA at least once in their lifetime.⁴ Data from the Treatment Episode Data Set, a national database obtained from admissions to substance abuse treatment centers, recorded a twofold increase in admissions due to MA between 1997 and 2007,⁵ with 46% of patients treated for MA abuse being women.

Substance use by pregnant women continues to be a serious problem with 5.2% of pregnant women aged 15 to 44 years reporting the use of illicit drugs during pregnancy.⁴ The Infant Development, Environment and Lifestyle (IDEAL) Study, a longitudinal prospective cohort study to address the long-term effects of prenatal MA exposure, reported a 5.2% prevalence of MA use among women who participated in the study.⁶ Of further concern, over 40% of the women enrolled in the IDEAL study were still using MA during the third trimester, and approximately half did not significantly change their use during the course of their pregnancy.⁷

Preclinical models of prenatal MA exposure have shown deleterious MA-induced effects on both the mother and offspring. In addition to structural eye defects, delayed motor development, and learning impairments,⁸ growth restriction is also a consistent finding in animals exposed to prenatal MA.⁹ Exposure of pregnant rats to MA has been associated with shorter gestation periods,^{10,11} and MA-exposed pups also have lower birth weights^{8,12} and higher mortality rates than control rats.⁸

Similar to findings in animal models, prenatal MA exposure has been associated with newborn growth restriction. In a study of 105 mother–infant pairs with positive results of urine toxicology screens at the time of delivery, Oro and Dixon found that in comparison to narcotic-exposed neonates, MA/cocaine-exposed neonates were more likely to have decreased birth weight and head circumference and to be small for gestational age (SGA).¹³ A retrospective review of MA-exposed neonates reported an increased incidence of SGA¹⁴ relative to unexposed newborns. In a study of 65 children born to mothers in Sweden who had abused amphetamines during their pregnancy, the mean birth weight, height, and head circumference were below the means of their unexposed peers.¹⁵

Although previous clinical studies have examined the association of MA with neonatal growth restriction, relatively little is known about its effects on postnatal growth. In a sample of 65 women in Sweden who abused amphetamines during their pregnancy, the exposed children had decreased growth parameters at ages 1 and 4 years.¹⁶ By 10 years of age, exposed females remained shorter and lighter than their peers,¹⁶ whereas exposed males weighed significantly more than the national standard in Sweden by age 14 years.¹⁷ These longitudinal findings are limited by the exposed children being compared with an unselected community sample instead of a matched comparison group and because coexposures to other drugs including opiates were prevalent in the MA group but not known in the unselected sample. Further, all studies rely solely on maternal self-reporting for drug use. The prospective, longitudinal IDEAL study is, to our knowledge, the first large-scale, matched, prospective investigation examining the effects of prenatal MA exposure. We have previously reported that MA-exposed newborns had a higher incidence of being SGA.¹⁸ We designed this study to address the longitudinal effects of intrauterine MA exposure on physical growth from birth to 36 months of age.

Study Design

Detailed methods for the IDEAL study have been previously reported.¹⁹ In brief, recruitment took place over a 2-year period from August 1, 2002 until November 30, 2004 at four clinical sites in specific geographic areas with prevalent MA use. The study was approved by the Institutional Review Boards at all participating sites. A National Institute on

Drug Abuse Certificate of Confidentiality was obtained for the project that ensured confidentiality of information regarding maternal drug use but did not exclude reporting evidence of child abuse or neglect.

Participants

IDEAL screened 34,833 mother–infant pairs at the time of the infant’s birth, of which 17,961 (52%) were eligible, 9038 (26%) were ineligible, and 7834 (22%) were not available to be approached and screened for eligibility. Of the 17,961 eligible subjects, 3705 (21%) consented for participation in the study. Only mothers with prenatal MA use ($n = 204$) and their matched comparisons ($n = 208$) were enrolled in the longitudinal study. Comparison subjects (COMP) were matched on race, birth weight category (< 1500 g, 1500 to 2500 g, >2500 g), maternal education, and type of insurance as proxy for socioeconomic status (SES). Growth parameters were collected at birth, 12, 24, and 36 months. Subjects with growth parameter data for at least two of the three study visit were included ($n = 176$ MA; $n = 175$ COMP). Growth parameter data were collected for all available subjects at each time point in the follow-up study. The nonexposed subjects from the comparison group had nearly complete data for birth length and birth head circumference. Birth length was missing for one nonexposed subject, and birth head circumference was missing for two MA-exposed subjects and two nonexposed subjects. At 12 months ($n = 330$), length was missing for one MA-exposed subject. At 24 months ($n = 283$), length was missing for three MA-exposed subjects and one nonexposed subject. At 36 months ($n = 254$), length was missing for three MA-exposed subjects and one non-exposed subject.

Exposure to opiates, LSD and PCP were excluded based on previous cocaine studies suggesting those drugs as confounding variables. Both groups included prenatal alcohol, tobacco, and marijuana use as background variables. Based on epidemiology at the time of recruitment, which indicated that some MA users also used cocaine, subjects exposed to cocaine along with MA were included in this study. Of the 176 MA subjects, 16 (9.1%) were also exposed to cocaine. Preliminary analyses of these subjects did not reveal any differences in birth weight or prevalence of SGA between the MA-only group and those who were also exposed to cocaine ($p > 0.05$ in both cases). Thus, those subjects with both MA and cocaine exposure were included in the analyses. There were no cocaine-related differences in gestational age, birth length, or birth weight for length in this study.

Procedures

Once informed consent was obtained, maternal interviews were conducted using the Lifestyle Interview to determine prenatal drug use.⁶ Maternal and neonatal medical chart reviews were completed, and meconium was collected in the nursery from all infants whose mother gave consent. Information on the collection procedures and analysis of the meconium samples was published previously.¹⁹ Briefly, the samples were collected in the nursery and shipped to a central laboratory (United States Drug Testing Laboratory) for analysis of amphetamines, cocaine metabolites, cannabinoids, opiates, and cotinine. The specimen is screened initially with a sensitive enzyme multiplied immunoassay test (EMIT II; Dade-Behring, Cupertino, CA). If positive results are obtained, the specific drug analyte or metabolite is confirmed by gas chromatography–mass spectrometry (GC/MS). Exposed subjects were identified by maternal report of MA use during the pregnancy on the basis of the hospital interview and/or GC/MS confirmation of amphetamine and metabolites in infant meconium. Unexposed subjects were defined as denial of MA use during this pregnancy and negative GC/MS results for amphetamine and metabolites.

Gestational age was determined by estimated date of confinement for women with adequate prenatal care (five or more visits). Prenatal gestational age was determined from the

mother's medical chart and was based on mother's last menstrual period, an early ultrasound, and the clinical exam during prenatal care. If there was no "best obstetric estimate" in the chart, the postnatal estimate of gestational age was the physician's estimate of gestational age at the time of delivery. In the few instances where there was a significant discrepancy between obstetric dating and the postnatal gestational assessment, the postnatal examination performed by the subject's physician was utilized. For women with no or inadequate prenatal care, the postnatal examination by the patient's physician was used for gestational dating. These examinations were performed by skilled clinicians trained in these examinations. SGA, defined as growth parameters < 10th percentile for standard growth curves, was calculated using Alexander's algorithm.²⁰

Stature was recorded in inches to the nearest decimal and weight to the nearest 0.1 kg on a balanced scale by trained study staff using standard equipment and standard methods, with children wearing socks, no shoes, and light clothing. The occipital-frontal head circumference was measured with a standard flexible nonstretchable measuring tape placed over the occiput and the supraorbital ridges. Measurements were also recorded in inches to the nearest decimal. Length and head circumference were each measured three times to ensure accuracy. Measurements were averaged if there was a discrepancy. All measurements were collected by trained examiners blinded to MA exposure status. Weight-for-length percentiles were analyzed as a proxy for body mass index.

Statistical Analysis

Growth parameters for all children attending at least two of the three annual visits were included in the analysis. SAS PROC MIXED (version 9.1.3, SAS Institute, Cary, NC) was used to fit individual growth models to examine the effects of prenatal MA exposure and prematurity on growth trajectories after controlling for covariates. PROC MIXED uses a likelihood-based estimation method that can accommodate data that are missing at random. The advantage to this approach is that all available data are used in the analysis and subjects with missing data are not ignored. In these longitudinal models, a random intercept and unstructured covariance were specified to account for within-subject variation over time. All models took into account the cluster effect of subjects within study site.

All analyses were adjusted for covariates. Covariates were selected based on conceptual reasons, published literature, and maternal characteristics that differed between groups if not highly correlated with other covariates. Covariates included in analyses were recruitment site, partner status, and prematurity. Prematurity was included in the final models because it was associated with MA exposure and growth outcomes at $p < 0.10$. Partner status met the criteria initially but was removed from the final models as it did not display any significant contribution ($p > 0.10$). Candidate covariates examined but not included in the final analyses were prenatal exposure to tobacco, alcohol, and marijuana; family SES at birth; gender; maternal prepregnancy and pregnancy weight gain; and maternal age. These covariates either failed to meet the empirical association criteria or did not have a significant association with the outcome. Maternal hypertension and diabetes mellitus were not considered as potential covariates because the medical chart review used in our study captured only insulin-dependent diabetes and chronic hypertension and may have underestimated cases of both of these conditions. The current sample has 8 of 351 subjects with insulin-dependent diabetes, and there were also only eight subjects with chronic hypertension.

Adjusted values for height by age and MA exposure were generated using height z scores by age and gender calculated from the Centers for Disease Control growth chart algorithm.²¹ The most commonly used clinical indicator to assess size and growth patterns of individual children are percentiles. The z score is the deviation of the value for an individual from the

mean value of the reference population divided by the standard deviation for the reference population. *Z* scores have a direct relationship with percentiles. *Z* scores take into account the distribution of the anthropometric measures within the population more accurately.²²

Post hoc power analyses were calculated using power analysis for repeated measures designs in SPSS.²³ Power was calculated using an $n = 250$ (number of subjects with data for length at 3 years). Power of 1.0 was obtained in this sample.

Results

Maternal characteristics of the 351 mother–infant pairs attending at least two of the three annual visits are shown in Table 1. No differences were found in the matched characteristics for race, type of insurance, maternal education, or maternal age. Despite matching for education and public insurance as proxies for SES, the MA-using mothers were still more likely to be of lower SES. The MA-using women had fewer prenatal care visits and were more likely to use tobacco, alcohol, and marijuana than the COMP group. Neither maternal height nor prepregnancy weight differed between the groups, though maternal weight gain was significantly higher in the exposed group.

There were no differences between the groups with regards to newborn gender, birth weight, incidence of SGA, or birth weight < 2500 g (Table 2). In the full follow-up sample, SGA was more prevalent in MA versus COMP (16.7% versus 10.1%, $p = 0.050$). There was no differential attrition with respect to SGA for the subsample ($n = 351$) versus the subjects not included ($n = 61$; 13.7% versus 11.5%, $p = 0.641$).

Of the 351 subjects included in the analysis, the exposed infants had decreased height and head circumference, lower gestational age, and an increased incidence of birth < 36 weeks' gestation relative to the COMP group (Table 2).

Growth trajectories for weight, weight-for-length, height, and head circumference of the MA and COMP groups were examined over the first 36 months of age. The MA group had a lower height trajectory throughout the first 3 years of life compared with the COMP group ($p = 0.021$; Fig. 1). Children in the COMP group were on average 0.63 cm longer (standard error [SE] = 0.27) than those in the MA group ($p = 0.021$) over the 3-year trajectory. At birth, the MA group height in centimeters was 49.82 ± 0.25 , whereas the COMP group height was 50.97 ± 0.21 . At 1 year, the MA group height was 75.56 ± 0.26 , and the COMP group height was 75.74 ± 0.25 . At 2 years, the MA group height was 85.56 ± 0.31 , and the COMP group height was 86.68 ± 0.36 . At age 3, the MA group height was 94.45 ± 0.36 , and the COMP group height was 94.92 ± 0.39 . Despite the lower height scores in the MA group, by age 3, children in both groups were growing at roughly the same rate per month (2.27 cm, SE = 0.02). It is expected that this growth rate will slow down as the children age (Beta = -0.030 , $p < 0.0001$).

Given the exposed newborns were more likely to be born at < 36 weeks' gestation, separate growth analyses were conducted for the term-only sample ($n = 301$). The adjusted height trajectory in the MA term-only group was lower compared with the COMP term-only group ($p = 0.034$; Fig. 2). After adjusting for covariates, the COMP term-only infants were on average 0.62 cm (SE = 0.29) longer than the MA term-only group ($p = 0.034$) over the 3-year trajectory. Similar to the full sample, by age 3, both the MA and COMP term-only were growing at approximately the same rate per month (2.25 cm, SE = 0.02).

Growth trajectories of all the preterm infants were also analyzed and adjusted for covariates. On average, the preterm infants were 4.05 cm (SE = 0.43) shorter than term infants ($p <$

0.0001) but displayed a steeper height trajectory from the full sample by growing on average 0.093 cm (SE = 0.021) more per month than the term infants ($p < 0.0001$).

No differences were found in weight, head circumference, and weight-for-length growth trajectories between the MA and COMP groups for the full sample, term-only, and preterm-only subsamples. Additionally, no significant drug interaction effects were found on child growth trajectories.

Discussion

We report decreased height trajectories in MA-exposed children through the first 3 years of life. Growth deficits associated with prenatal MA exposure have been reported previously in the preclinical rat model as well as MA-exposed children. Decreased birth weights in rats have been observed with MA exposure throughout gestation¹² as well as in rats exposed to MA during the third-trimester equivalent.²⁴ As the rat offspring aged, the body weights in the exposed group remained lower, though differences were less pronounced.²⁴ We reported previously that MA-exposed newborns were at increased risk for being born SGA.^{18,19} These SGA findings were adjusted for factors including prenatal tobacco, alcohol, and marijuana use, suggesting direct MA-induced growth-restrictive effects on the developing fetus.

Our findings of decreased height trajectory over the first 3 years of life are also consistent with previous reports of height deficits in MA-exposed children at birth and at 1 and 4 years of age.¹⁵ It is unclear if our findings of decreased height trajectory will impact height in later childhood or adult height. In the only previous study to follow children into adolescence, MA-exposed males were actually found to be taller and heavier than their peers by 14 years of age with no differences noted in the exposed females.¹⁷ However, this study was limited by small sample size and the lack of an adequate control group.

Insights into long-term growth effects after MA exposure may be gained from studies of children exposed to cocaine, another sympathomimetic agent. The targeted deficit in height we report is consistent with the work of Covington and colleagues, who after accounting for other prenatal drug exposures found children prenatally exposed to cocaine were up to 1 inch shorter and twice as likely to fall below the 10th percentile in height as control children at age 7 years.²⁵ Minnes and colleagues reported greater cocaine exposure in utero predicted lower height for age z scores by age 6 years.²⁶ Another report in a longitudinal study of cocaine- and alcohol-exposed children up to age 8 years affirmed growth deficits, with the majority of the growth parameters mostly resolved by 6 months of age.²⁷ Because tall stature carries with it certain social advantages, including advancements in professional settings, increased earnings, and social dominance,^{28,29} findings of diminishing differences in growth parameters later in childhood are reassuring.

There are numerous possible etiologies for decreased growth parameters following prenatal MA exposure. Maternal morbidities associated with MA, including hypertension and placental abnormalities, can adversely affect fetal growth.^{9,13} Growth retardation specifically targeting height in the MA-exposed children may also be due to interference with cartilage metabolism.³⁰ MA has an inhibitory effect on mineral uptake by cartilage in vitro as well as a marked reduction in the activity of enzymes involved in the biosynthetic pathway.³⁰ As such, direct inhibitory effects on cartilage growth may interfere with bone growth, ultimately leading to shorter stature in the exposed children. Further, cocaine has been shown to impair placental transport of amino acids, which also may be a mechanism for growth impairment with MA.³¹

Researchers have found polydrug exposure may impact growth parameters,³² however, despite a significant increase in alcohol, tobacco, and marijuana use by the exposed group, our findings are consistent with previous results. Prenatal alcohol exposure has been associated with decreased growth parameters through 3 years of age.³³ Although prenatal tobacco exposure has been associated with decreased growth parameters at birth, growth deficits were no longer significant by 6 years of age or during adolescence.^{34,35} Children exposed to marijuana have been found to be heavier and taller than the unexposed children, with differences dissipating by 4 years of age.³⁶

Due to MA's anorectic characteristic, it is often associated with decreased weight and a lack of nutrition. Conversely, in the current study, mothers in the exposed group gained more weight than those in the comparison group. Although MA is an anorectic agent, discontinuing MA use often leads to a rapid increase in weight, a possible explanation for why the exposed mothers gained more weight during pregnancy.

We evaluated weight-for-length trajectories as a proxy for body mass index and found no differences in the MA-exposed children up to age 3. These findings are reassuring given the association between fetal growth restriction and long-term health problems in adulthood initially described by Barker and colleagues, who demonstrated a strong relationship between decreased birth size and postnatal growth with development of illnesses including diabetes and cardiovascular disease in later life.³⁷ It is further reassuring that head circumference trajectories were comparable in both groups as sparing of head circumference in growth-restricted children is not associated with developmental delay.³⁸

There are several limitations to our study, and therefore, our findings should be interpreted with caution. Despite matching based on birth weight, there were more newborns 36 weeks' gestation in the exposed group. However, when only term newborns were analyzed, decreased height trajectory was still observed in the MA group, suggesting prematurity was not the primary factor influencing the lower height velocity. Despite matching for proxies of SES, the exposed group was more likely to have a lower SES, which may have increased the risk of food scarcity and decreased optimal nutritional intake. However, nutritional deprivation is associated with decreased weight as well as height, which we did not observe. Paternal height information was not available and parental height is a significant predictor of child height.³⁹ Because there is no reason to believe paternal height was unevenly distributed between the groups, paternal height is unlikely to be contributing to the decreased height velocity findings. Additionally, we did not examine whether the amount or frequency of MA exposure or if specific obstetric conditions such as maternal hypertension and diabetes impacted the growth trajectories. The current study also only includes children who attended at least two of the three visits, thus our sample size is reduced and may impact our power to answer additional questions.

In summary, we found decreased height trajectories throughout the first 3 years of life in MA-exposed children. However, there were no differences in head circumference, weight, or weight-for-length trajectories, suggesting that although exposed children demonstrate continued height growth restriction, the impaired growth is not placing them at an increased risk for developmental delay or later onset of cardiovascular morbidity. Long-term follow-up will determine if the decreased height trajectories in MA-exposed children continues into later childhood and affects final adult height. Additional investigation into the acute and long-term behavioral and neuropsychological effects of prenatal MA exposure on the developing infant and child are also necessary as birth and postnatal head circumference are only one factor impacting developmental delay.

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Figure 1.
The adjusted height trajectories of the methamphetamine-exposed and comparison children throughout the first 3 years of life (differences between the groups: $p = 0.021$).

Figure 2.

The adjusted height trajectories of only those children born at term in the methamphetamine-exposed and comparison group throughout the first 3 years of life (differences between the groups: $p = 0.034$).

Table 1**Maternal Characteristics by Methamphetamine Exposure**

	Exposed (<i>n</i> = 176), <i>n</i> (%) or Mean (SD)	Comparison (<i>n</i> = 175), <i>n</i> (%) or Mean (SD)	<i>p</i> Value
Race			0.862
White	67 (38.1%)	69 (39.4%)	
Hispanic	40 (22.7%)	38 (21.7%)	
Pacific Islander	30 (17.0%)	32 (18.3%)	
Asian	25 (14.2%)	22 (12.6%)	
Black	8 (4.5%)	10 (5.7%)	
American Indian	6 (3.4%)	3 (1.7%)	
Other	0 (0.0%)	1 (0.6%)	
Hollingshead SES level 5	59 (33.7%)	18 (10.3%)	< 0.001
Public insurance	157 (89.2%)	149 (85.1%)	0.074
No. of prenatal visits	11.3 (7.5)	14.5 (5.4)	< 0.001
Education < 12 y	83 (47.2%)	65 (37.1%)	0.057
Prenatal tobacco use	140 (79.5%)	44 (25.1%)	< 0.001
Prenatal alcohol use	65 (36.9%)	22 (12.6%)	< 0.001
Prenatal marijuana use	56 (31.8%)	7 (4.0%)	< 0.001
Maternal height (ft.)	5.35 (0.23)	5.32 (0.22)	0.255
Prepregnancy weight (lbs.)	142.1 (37.2)	145.0 (36.7)	0.459
Weight gain (lbs.)	42.9 (20.6)	33.6 (15.9)	< 0.001
Age (y)	25.6 (5.7)	24.6 (5.5)	0.092

SD, standard deviation; SES, socioeconomic status.

Table 2

Newborn Characteristics

	Exposed (<i>n</i> = 176), <i>n</i> (%) or Mean (SD)	Comparison (<i>n</i> = 175), <i>n</i> (%) or Mean (SD)	<i>p</i> Value
Gender (male)	96 (54.5%)	92 (52.6%)	0.711
Birth weight (g)	3187.9 (624.1)	3293.1 (571.8)	0.101
Height (cm)	49.8 (3.6)	51.0 (3.0)	0.001
Head circumference (cm)	33.7 (1.8)	34.1 (1.8)	0.032
Gestational age	38.2 (2.3)	39.0 (1.8)	0.001
SGA	27 (15.3%)	21 (12.0%)	0.362
Low birth (< 2500)	22 (12.5%)	21 (12.0%)	0.886
Preterm (= 36 wk)	35 (19.9%)	15 (8.6%)	0.002

SD, standard deviation; SGA, small for gestational age.