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Prenatal Methamphetamine Exposure and Neonatal and Infant Neurobehavioral Outcome: Results from the IDEAL Study

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Abstract

Background—Methamphetamine (MA) use among pregnant women is an increasing problem in the United States. How MA use during pregnancy affects neonatal and infant neurobehavior is unknown.

Methods—The Infant Development, Environment, and Lifestyle (IDEAL) study screened 34,833 subjects at 4 clinical centers. 17,961 were eligible and 3,705 were consented, among which 412 were enrolled for longitudinal follow-up. Exposed subjects were identified by self-report and/or GC/MS confirmation of amphetamine and metabolites in meconium. Comparison subjects were matched (race, birth weight, maternal education, insurance), denied amphetamine use and had a negative meconium screen. Both groups included prenatal alcohol, tobacco and marijuana use, but excluded use of opiates, lysergic acid diethylamide, or phencyclidine. The NICU Network Neurobehavioral Scale (NNNS) was administered within the first 5 days of life and again at one month to 380 enrollees (185 exposed, 195 comparison). ANOVA tested exposure effects on NNNS summary scores at birth and one month. GLM repeated measures analysis assessed the effect of MA exposure over time on the NNNS scores with and without covariates.

Results—By one month of age, both groups demonstrated higher quality of movement (P=.029), less lethargy (P=.001), and fewer asymmetric reflexes (P=.012), with no significant differences in NNNS scores between the exposed and comparison groups. Over the first month of life, arousal increased in exposed infants but decreased in comparison infants (p=.031) and total stress was decreased in exposed infants with no change in comparison infants (p=.026).

Conclusions—Improvement in total stress and arousal were observed in MA-exposed newborns by one month of age relative to the newborn period.

INTRODUCTION

Methamphetamine (MA) abuse is a significant problem in the United States, particularly in the West and Midwest. Worldwide, amphetamines are second only to cannabis as the most widely abused drugs, with a prevalence of 14 to 57 million, or 0.3 to 1.3%, of all 15-64 year olds(1). In 2010, an estimated 353,000 people age 12 or older in the United States reported using MA, with 105,000 estimated new users(2). Women account for a substantial subset of MA users; data from treatment centers in 2003 showed 45% of patients treated for amphetamine abuse were women(3), increasing to 46% in 2009(4). Seven percent of women admitted to treatment centers in 2009 abused MA at time of admission(5). Moreover, MA abuse among pregnant women is a persistent problem. The Infant Development, Environment and Lifestyle (IDEAL) study found approximately 6% of women reported drug use during pregnancy(6). Further, the prevalence of MA abuse in pregnant women admitted

to federally funded treatment centers in the U.S. rose to 24% in 2006(7). Similarly, international data from 2004 demonstrates that amphetamines were used by 23% of substance-abusing mothers(8).

The effects of prenatal MA exposure on childhood outcome are not well characterized. MRI data has shown that MA exposure is associated with reductions in striatal and caudate volume, which may be associated with cognitive deficits(9). Volumetric assessments of MRIs in exposed children have also demonstrated smaller subcortical volumes including the putamen, globus pallidus, and hippocampus, potentially impacting attention and memory(10). These findings are consistent with behavioral issues described in a small cohort of children exposed to methamphetamine. In this small non-randomized sample, prenatal MA exposure is associated with deficits in executive function and spatial performance(11), aggressive behavior and problems with peers(12), as well as delays in math and language(13).

Relatively little is known about the effects of MA during early infancy. In a study of cocaine and MA exposed newborns, there was an increased incidence of intraventricular hemorrhage and white matter densities observed on cranial ultrasound(14). In another study, prenatal amphetamine exposure has been associated with increased drowsiness in exposed infants in the first few months of life that resolved by twelve months of age(15). However, these previous findings were retrospective and utilized a small sample size. The Infant Development, Environment and Lifestyle (IDEAL) study is a prospective longitudinal investigation of neurobehavioral outcome related to MA exposure *in utero*. Infant neurobehavior was assessed with the NICU Network Neurobehavioral Scale (NNNS), a measures that strongly correlates with scores on the 12 and 24 month Bayley exam in neonates born <37 weeks' gestation(16). We previously reported preliminary data from the IDEAL study demonstrating that exposed neonates have decreased arousal, increased stress, and poor quality of movement at birth(17). This study reports neurobehavioral findings from the complete cohort of enrolled neonates in the IDEAL study. Further, this report presents findings in one month old infants to determine if the differences reported at birth improved or remained unchanged by early infancy.

METHODS

Study Design

The IDEAL study is a multi-site, longitudinal study investigating the effects of prenatal MA exposure on child outcome. Detailed recruitment methods for the IDEAL study have been reported previously(18). In short, from September 2002 - November 2004, subjects were recruited at the time of delivery from seven hospitals in four geographically diverse, collaborating centers in the following areas: Los Angeles, CA; Des Moines, IA; Tulsa, OK; and Honolulu, HI. All women delivering at each of the four clinical sites were approached (n=26,999), screened for eligibility (n=17,961), and consented to participate (n=3,705). A postpartum mother was excluded if she was <18 years of age; used opiates, lysergic acid diethylamide, phencyclidine or cocaine-only during her pregnancy; or was non-English speaking. Further, a mother was excluded if she had a history of hospitalization for intellectual disability or emotional disorders, or was overtly psychotic or had a documented history of psychosis; Exclusion criteria for the infants included: critically ill and unlikely to survive, multiple birth, major life threatening congenital anomaly, documented chromosomal abnormality associated with mental or neurological deficiency, overt clinical evidence of an intrauterine infection, and sibling previously enrolled in the IDEAL study.

MA exposure was determined by self-reported use during this pregnancy and/or a positive meconium screen and gas chromatography/mass spectroscopy (GC/MS) confirmation.

Comparison subjects were defined as denial of MA use during this pregnancy and a negative GC/MS for amphetamine and metabolites.

The study was approved by the Institutional Review Boards at all participating sites (Iowa Health-Des Moines, the University of Oklahoma, Hillcrest Medical Center, St. Francis Health System for St. Francis Hospital, St. John Medical Center, Hawaii Pacific Health for Kapiolani Medical Center for Women & Children, Harbor-UCLA Medical Center, Long Beach Memorial Medical Center), and signed informed consent was obtained from all subjects. A National Institute on Drug Abuse Certificate of Confidentiality was obtained for the project that assured confidentiality of information regarding the mothers' drug use, superseding mandatory reporting of illegal substance use.

Participants

The longitudinal follow-up sample included all MA-exposed infants and mothers (n=204) and comparison dyads (n=208) matched on maternal race, birth weight, type of insurance, and education. Because we are analyzing the effect of MA exposure on the neonate and at one month, only subjects who were available for both assessments were included in the analysis (exposed n=185, comparison n=195).

Procedures

After consent was obtained, a medical chart review and a recruitment Lifestyle Interview(19, 20) were performed to acquire information about prenatal substance use, maternal characteristics and newborn characteristics. Socioeconomic status (SES) was determined using Hollingshead scale, an index that ranks SES based on occupation and years of education(21). Meconium was collected in the nursery on all infants of consented mothers. Information on the collection procedures and analysis of the meconium samples has been previously published(18).

The NNNS exam was administered to all subjects born at term within the first 5 days of life by certified examiners masked to MA exposure status. Subsequently, the exam was performed again at one month of age. The NNNS is a standardized neurobehavioral exam for both healthy and at-risk infants that provides an assessment of neurological, behavioral, and stress/abstinence neurobehavioral functioning(22). The neurological component includes active and passive tone, primitive reflexes, and items that reflect the integrity of the central nervous system and maturity of the infant. The behavioral component is based on items from the Neonatal Behavioral Assessment Scale(23), modified to be sensitive to presumed drug effects. The stress/abstinence component is a checklist of "yes" or "no" items organized by organ system based primarily on the work of Finnegan(24).

The NNNS items are summarized into the following scales: Habituation, Attention, Arousal, Regulation, Handling, Quality of Movement, Excitability, Lethargy, Nonoptimal Reflexes, Asymmetric Reflexes, Hypertonicity, Hypotonicity, and Stress/Abstinence.

Statistical Analysis

Analysis of variance (ANOVA) and chi-square analyses were used to compare the MA-exposed and comparison newborn groups on medical and demographic characteristics, as well as the twelve NNNS summary scores for MA exposure effects. These analyses were repeated with the one-month NNNS summary scores.

MA exposure effects were examined using General Linear Modeling (GLM) for repeated measurements of NNNS summary scores over time, after adjustment for covariates, including maternal drug coexposures (see "Standard Covariate Set"). This approach

considers the within-subjects factor (time), the between-subjects factor (exposure status), and an interaction effect (time by exposure status). Habituation was not analyzed, as too few infants were sleeping at the start of the exam. Significance was accepted at $p<0.05$. Data were analyzed using SPSS for Windows (Rel. 17.0.0 2008 Chicago: SPSS Inc.).

Standard Covariate Set

Covariates were selected based on conceptual reasons, published literature, and maternal and newborn characteristics that differed between groups if not highly correlated with other covariates. The effect of prenatal alcohol, tobacco, and marijuana exposure on NNNS measures and birth weight have been previously reported(19, 25). The covariates included were heavy prenatal alcohol, tobacco, and marijuana use; Hollingshead socioeconomic status; birth weight; first born; and recruitment site. Heavy use was defined based on thresholds for detecting effects that have been previously reported(26, 27, 27-31). Heavy alcohol use was defined as ≥0.5 oz of absolute alcohol per day (1 standard drink). For tobacco, heavy use was defined as ≥10 cigarettes per day. Heavy marijuana use was defined as ≥0.5 joints per day. Assessment of first born utilized dichotomous [yes/no] variables. SES and birth weight were continuous variables.

RESULTS

Maternal and Newborn Characteristics

The maternal characteristics are shown in Table 1. As expected, there were no differences between the groups in race or maternal education, as these characteristics were matched in our study design. However, despite controlling for maternal education, mothers who used MA were still less likely to have an annual income greater than $10,000. In addition, MA-abusing mothers were more likely to be single and older. Furthermore, these mothers also had fewer, as well as later, prenatal visits. Finally, the mothers of exposed infants were more likely to use tobacco, alcohol, and marijuana during their pregnancy, and were more likely to be heavy abusers of these substances in contrast to the mothers of the comparison group.

The infant characteristics are presented in Table 2. The exposed infants were generally full term but born 1 week earlier than the comparison infants. There were no differences in gender or birth weight, but the exposed newborns had shorter lengths and smaller head circumferences in contrast to the comparison newborns. The exposed infants were more likely to have a lower 1 minute Apgar score but no differences were noted in Apgar scores by 5 minutes. Lastly, the exposed infants were more likely than the comparisons to be the first born.

Neurodevelopmental Outcome on the NNNS

After adjustment for covariates, we found significant main effects of time, showing higher arousal ($p=.002$) and quality of movement ($p=.029$), and reduced lethargy ($p=.001$) and asymmetric reflexes ($p=.012$) from birth to one month (Table 3). No significant main effects of exposure were observed. However, significant interactions between exposure and time were found for arousal and total stress. In regards to arousal, the estimated marginal mean for the comparison condition declined over the first month of life, whereas the mean slightly increased for the MA-exposed infants ($p=.031$). In regards to total stress, the MA-exposed infants showed a steeper decline in stress than comparison infants, such that the estimated marginal means at one-month were essentially equivalent ($p=.026$).

DISCUSSION

This is the first prospective investigation reporting the effects of prenatal MA exposure on neurobehavioral outcome at birth and one month. We found presumed maturational changes in all infants, regardless of exposure status, in quality of movement, lethargy, and asymmetric reflexes. In addition, by one month, the MA-exposed infants showed no difference in arousal and total stress relative to the control group.

The overall arousal scores in the MA-exposed infants increased over the first month of life, indicating that by one month of age these infants were generally less drowsy. These findings compliment previous findings regarding drowsiness in exposed infants at birth that resolved by twelve months of age(32). In contrast, the Maternal Lifestyle Study, which evaluated the neurodevelopmental effects of prenatal cocaine exposure using the NNNS, found lower arousal in the cocaine-exposed infants at one month of age(19). MA is commonly compared to cocaine due to their similar mechanisms of action as sympathomimetic agents. However, the effects of MA are thought to be potentially greater given its significantly longer half-life and ability to function not only as a dopamine and a norepinephrine reuptake inhibitor, but as a catecholamine release trigger as well. Further, we found a decrease in total stress among the MA-exposed neonates over the first month of life. Our findings in regards to stress have significant implications, particularly in the context of risk factors for non-accidental trauma. Specifically, the association of parental illicit and legal drug abuse as a substantial risk factor for non-accidental trauma is well described(33-35); this has significant implications for our exposed infants given the high risk environment into which they are immersed. Likewise, infants who are stressed are at an even higher risk for child abuse given the additional strain placed on their caregivers(36, 37). The reduction of stress signs in the MA-exposed infants alleviates some of the concern that MA exposure affects infant temperament in such a way that, compounded with the environmental risk, would increase their risk of non-accidental trauma.

No significant differences from newborn to one month were found based solely on exposure status. This is in contrast to studies on other illicit and legal drugs which report differences at birth as well as later in life. Prenatal nicotine exposure has been associated with increased excitability, hypertonicity, need for handling and stress/abstinence scores at birth(25), with increased need for handling persisting to one month of age(38). Prenatal cocaine exposure has been associated with increased central nervous system stress, poor visual and auditory following, hypertonicity, and drowsiness at birth(39), as well as lower arousal, lower regulation, and higher excitability at one month(19). Our inability to show significant differences based on exposure status may be explained by the overall high risk of both groups. We matched each subject based on SES and race, but our statistical capacity for controlling covariates is not limitless; therefore it is possible that both groups have sufficient risk that affects their functioning. Although differences attributable to MA exposure at birth may resolve at one month of age, it is important to continue following these children as they develop to monitor whether latent neurobehavioral effects emerge during childhood.

Our results should be interpreted with caution, as there are limitations to our study. First, the exposed group of subjects was selected primarily based on self-report. However, the reported use of alcohol, tobacco and marijuana is consistent with national surveillance data and only six subjects were ascertained by GC/MS without also having self-reported. Since meconium production begins at 14-16 weeks' gestation, meconium testing primarily reflects maternal drug use only during the second and third trimesters(40), but recent evidence show that the assay for MA analytes may not reveal known use until the third trimester(41). Therefore, information regarding drug use in the first and second trimester could only be obtained by self-report. Additionally, this report does not evaluate for dose-response effects.

While we found no significant differences in NNNS summary scores between the two groups overall, if we specifically evaluated the heavily exposed neonates the effects may be augmented. Similarly, this report also does not evaluate for differences based on exposure timing, although our preliminary report does describe findings of elevated stress abstinence related to first trimester exposure and poorer quality of movement associated wtih versus third trimester exposure(17).

In summary, we found subtle neurobehavioral improvements by one month of age in infants exposed to MA *in utero*, which has both short and long-term implications. Despite not finding persistent neurobehavioral differences from birth to one month, these exposed infants are susceptible to numerous risk factors related to both direct and indirect effects of MA exposure. These risks include parental abuse, parental neglect, and exposure to chemicals involved in making MA in the home(42), which may lead to significant neurobehavioral issues in childhood and later in life. These at-risk newborns may require positive caregiving environments and interventions to potentially prevent long-term, permanent insults. Long term follow-up is required to detect and possibly prevent exacerbation of these subtle effects beyond infancy.

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Table 1

Maternal characteristics of methamphetamine-exposed and comparison groups

	Number (Percent) or Mean (SD)	
	Exposed (*N*=185)	**Comparison (*N*=195)**
Race / Ethnicity		
White	71 (38%)	78 (40%)
Hispanic	40 (22%)	41 (21%)
Hawaiian / Pacific Islander	34 (18%)	32 (16%)
Asian	25 (14%)	27 (14%)
Black	9 (5%)	12 (6%)
Other	6 (3%)	5 (3%)
Low SES (Hollingshead V)	60 (33%)*	22 (11%)
Household income <10,000	59 (36%)†	38 (20%)
No partner	103 (56%)*	68 (35%)
Education < high school	82 (45%)	73 (38%)
Maternal age, yr	25.8 (5.7)†	24.6 (5.5)
Gestational Age at 1st prenatal visit, week	14.6 (8.2)*	9.4 (5.7)
Number of prenatal visits	11.4 (7.3)*	14.2 (5.5)
Prenatal heavy METH use[a]	32 (18%)*	0
Prenatal tobacco use	148 (80%)*	53 (27%)
Heavy tobacco use	56 (30%)*	15 (8%)
# of cigarettes per day	7.0 (8.3)†	1.8 (4.8)
Prenatal alcohol use	69 (37%)*	25 (13%)
Heavy alcohol use	11 (6%)*	0
Ounces of absolute alcohol per day	0.12 (0.50)†	0.003 (0.02)
Prenatal marijuana use	61 (33%)*	8 (4%)
Heavy marijuana use	20 (11%)†	5 (3%)
Number of joints per day	0.15 (0.37)	0.10 (1.1)

* P<0.001,

† P<0.01

a use ≥3 times/week throughout pregnancy

Table 2

Newborn characteristics of methamphetamine and comparison groups

	Number (Percent) or Mean (SD)	
	Exposed (*N*=185)	**Comparison (*N*=195)**
Gestational age, week	38.3 (2.3)*	39.0 (1.8)
Birth weight, g	3194 (618)	3294 (569)
Length, cm	50.0 (3.4)*	51.0 (3.0)
Head circumference, cm	33.7 (1.8)*	34.1 (1.8)
Apgar, 1 min, <5	9 (4.9%)*	2 (1.0%)
Apgar, 5 min, <5	0	0
Male	100 (54%)	102 (52%)
First born	45 (24%)*	77 (39%)

* $P < 0.01$

Table 3

NNNS summary scores by methamphetamine exposure status and time of infant evaluation

	Birth Mean (SD) (*N*=380)		1 month Mean (SD) (*N*=380)		Exposure *p*		Time *p*		Interaction *p*	
NNNS items	**Exposed (*N*=185)**	**Comparison (*N*=195)**	**Exposed (*N*=185)**	**Comparison (*N*=195)**	**Unadj.**	**Adj.**	**Unadj.**	**Adj.**	**Unadj.**	**Adj.**
Attention	5.17 (1.04)	5.15 (1.17)	5.62 (0.98)	5.65 (1.01)	0.929	0.708	0.001	0.382	0.535	0.743
Arousal	3.92 (0.64)	4.12 (0.61)	4.09 (0.64)	4.02 (0.66)	0.170	0.701	0.359	**0.002**	0.002	**0.031**
Regulation	5.45 (0.65)	5.45 (0.73)	5.79 (0.70)	5.78 (0.67)	0.792	0.158	0.001	0.712	0.882	0.545
Handling	0.30 (0.23)	0.32 (0.25)	0.28 (0.27)	0.28 (0.26)	0.218	0.426	0.474	0.051	0.231	0.187
Quality of mvt.	4.37 (0.58)	4.48 (0.61)	4.87 (0.55)	4.87 (0.58)	0.194	0.222	0.001	**0.029**	0.150	0.159
Excitability	2.92 (1.91)	3.31 (1.86)	2.49 (1.86)	2.43 (2.03)	0.277	0.337	0.001	0.093	0.099	0.490
Lethargy	4.59 (2.51)	4.22 (2.49)	3.42 (1.61)	3.32 (1.22)	0.129	0.183	0.001	**0.001**	0.344	0.684
Extreme reflexes	0.33 (0.72)	0.42 (0.81)	0.35 (0.83)	0.43 (0.72)	0.261	0.914	0.134	0.172	0.047	0.673
Asymm. reflexes	0.38 (0.67)	0.27 (0.58)	0.37 (0.60)	0.30 (0.52)	0.053	0.095	0.761	**0.012**	0.570	0.586
Hypertonicity	0.03 (0.18)	0.03 (0.19)	0.15 (0.60)	0.12 (0.43)	0.528	0.366	0.001	0.363	0.675	0.528
Hypotonicity	0.15 (0.44)	0.12 (0.36)	0.04 (0.23)	0.08 (0.27)	0.859	0.981	0.002	0.072	0.230	0.794
Total stress	0.10 (0.05)	0.09 (0.05)	0.08 (0.05)	0.09 (0.06)	0.577	0.239	0.001	0.850	0.237	**0.026**