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Risk for Neurobehavioral Disinhibition in Prenatal Methamphetamine-Exposed Young Children with Positive Hair Toxicology Results

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Abstract

Background—The objective was to evaluate effects of prenatal methamphetamine exposure (PME) and postnatal drug exposures identified by child hair analysis on neurobehavioral disinhibition at 6.5 years of age.

Methods—Mother-infant pairs were enrolled in the Infant Development, Environment, and Lifestyle (IDEAL) Study in Los Angeles, Honolulu, Tulsa and Des Moines. PME was determined by maternal self-report and/or positive meconium results. At the 6.5-year follow-up visit, hair was collected and analyzed for methamphetamine, tobacco, cocaine, and cannabinoid markers. Child behavioral and executive function test scores were aggregated to evaluate child neurobehavioral disinhibition. Hierarchical linear regression models assessed the impact of PME, postnatal

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substances, and combined PME with postnatal drug exposures on the child's neurobehavioral disinhibition aggregate score. Past year caregiver substance use was compared to child hair results.

Results—A total of 264 children were evaluated. Significantly more PME children (n=133) had hair positive for methamphetamine/amphetamine (27.1% versus 8.4%) and nicotine/cotinine (38.3% versus 25.2%) than children without PME (n=131). Overall, no significant differences in analyte hair concentrations were noted between groups. Significant differences in behavioral and executive function were observed between children with and without PME. No independent effects of postnatal methamphetamine or tobacco exposure, identified by positive hair test, were noted and no additional neurobehavioral disinhibition was observed in PME children with postnatal drug exposures, as compared to PME children without postnatal exposure.

Conclusions—Child hair testing offered a non-invasive means to evaluate postnatal environmental drug exposure, although no effects from postnatal drug exposure alone were seen. PME, alone and in combination with postnatal drug exposures, was associated with behavioral and executive function deficits at 6.5 years.

Keywords

methamphetamine; hair; children; prenatal drug exposure; toxicology

Introduction

Prevalence of illicit amphetamines use is second only to cannabis worldwide.[1] While initiation of methamphetamine use remains stable,[2] methamphetamine treatment admissions[3] and manufacturing seizures continue to rise.[1] Methamphetamine laboratory incidents in the United States increased from 2007–2010.[4] In 2010 and 2011, many treatment facilities reported increased methamphetamine admissions over previous years.[5]

Methamphetamine is the primary substance reported by pregnant women in drug treatment facilities in the United States.[6] Behavioral therapies, such as cognitive-behavioral and contingency-management interventions, are common methamphetamine treatments.[7] Treatment facilities saw an 8–24% increase in admitted pregnant women seeking treatment for methamphetamine from 1994–2006,[6] and an increase in emergency room hospitalizations.[8] Despite 5.7% of pregnant women using methamphetamine,[9–10] most of what is known about the impact of prenatal methamphetamine exposure (PME) on development and child behavior derives from our Infant Development, Environment, and Lifestyle (IDEAL) study, the only longitudinal PME investigation. IDEAL study goals are to investigate outcomes associated with PME and understand the development of youth with both PME and early adversity to inform research, prevention, and intervention efforts. During infancy, the IDEAL study reported PME effects on poor fine motor performance, decreased arousal, and increased stress.[11] In 3–6.5 year-olds, PME was associated with executive function deficits[12] and behavior problems, including increased emotional reactivity, anxiousness, depressiveness, attention problems, withdrawn behavior,[13] and poor inhibitory control.[14]

PME can be identified through maternal self-report and/or biological analysis of methamphetamine markers in neonatal meconium, newborn hair, and placenta and umbilical cord tissue.[15–18] Postnatal exposure to environmental toxins and drugs of abuse in early childhood can be non-invasively detected by hair analysis. Hair testing offers advantages over more traditional drug monitoring matrices such as plasma or urine due to its long window of detection and non-invasive collection. Hair may test positive for drugs due to hair follicle drug incorporation from blood, deposition from sweat or sebum, and from environmental contamination.[19] Studies documenting child hair drug results are limited to parental custody or legal outcomes due to poisoning or exposure via an unsafe environment.[20–24] Hair testing in pre-adolescent children documents exposure, not seeking to differentiate systemic and environmental exposure.[20–24] Child hair illicit drug concentrations typically results from passive exposure to drug use in the home, accidental ingestion, or parental administration.[20] It is unclear what role environmental exposure to drugs of abuse plays in a child's development, and more specifically, in children with prenatal drug exposure. To date, no study examined the relationship between child hair drug findings and neurobehavioral outcomes in PME children.

Neurobehavioral disinhibition is a set of co-occurring problems including poor self-regulation, anxiety and affective disorders, cognitive impairment, and disruptive behavioral disorders.[25–26] Children and adolescents exhibiting these disinhibitory problems have longitudinal challenges including academic difficulties, delinquency, mental health problems, substance abuse, and juvenile justice system involvement.[25–27] Neurobehavioral disinhibition encompasses problems of excessive risk taking, impulsivity, aggression, irritability, difficult temperament, attention deficit-hyperactivity disorder (ADHD), impaired executive function, and poor behavioral control and emotional modulation.[25–28] The severity of neurobehavioral disinhibition in 8–14 year-olds was associated with maternal cocaine[27] and alcohol[28] use during pregnancy. Neurobehavioral disinhibition in these children also mediated substance use initiation by age 16–19.[27–28] In PME children, the IDEAL study demonstrated PME was associated with neurobehavioral disinhibition at 5 and 6.5 years of age.[12]

Our objectives were to characterize child hair toxicology results and assess agreement with caregiver self-reported drug use in the past year, and to evaluate independent and combined effects of prenatal methamphetamine and postnatal methamphetamine or tobacco exposure on child behavior, attention, and intelligence measures at 6.5 years.

Material and Methods

Participants

IDEAL subjects were enrolled at 4 study locations in the United States with high rates of methamphetamine use: Los Angeles, CA; Honolulu, HI; Des Moines, IA; and Tulsa, OK. The study was approved by Institutional Review Boards at each site and at the National Institute on Drug Abuse, and all participants provided written informed consent.[9]

Several thousand mother-infant pairs were screened at participating hospital sites during the 2-year enrollment period.[9] Initially, 3,708 pregnant mothers enrolled, with 204 PME infants

identified. Meconium from 3705 enrolled infants was screened by enzyme multiplied immunoassay technique (EMIT) or enzyme-linked immunosorbent assay (ELISA) for methamphetamine;[10] 3 infants had insufficient meconium for testing PME was identified by maternal self-reported methamphetamine use during pregnancy or confirmation of methamphetamine and metabolites in meconium by gas chromatography mass spectrometry (GC/MS) or liquid chromatography tandem mass spectrometry (LC-MS/MS).[16] Children were classified as having no PME when mothers denied methamphetamine use during pregnancy and their meconium screened negative for amphetamines and opiates. Employing a matched case control study design shortly after delivery when meconium analyses were complete, the 204 PME children were matched to 208 unexposed subjects on maternal race, private versus public insurance, maternal education (completed high school versus not completed), and infant birth weight category (<1500g, 1500–2500g, >2500g). Exclusionary criteria included maternal self-reported opiate or hallucinogen use and use of cocaine only.[9] This follow-up study at 6.5 years included 264 children; 133 with PME and 131 without PME. These children were selected as they were still enrolled and completed a 6.5-year study visit. Some children (n=35, 11.6%) did not have hair collected at their 6.5-year visit and were excluded from this follow-up study. Of the 35, 11 children had hair too short for collection, 9 caregivers or children refused hair collection, and 15 gave no other reason for no hair collection.

Caregivers completed a Lifestyle Interview and a Substance Use Inventory at birth and the 6.5 year follow-up visit.[29] These semi-structured interviews collected information on household composition, socioeconomic status (SES), home environment, neighborhood violence, family services received, changes in residency, domestic violence, and maternal drug use during the pregnancy of the enrolled child and during the year prior to the 6.5 year follow-up visit.[29] Caregivers also completed a physical growth questionnaire at the follow-up visit; child ADHD diagnoses and medications taken within the past year for this disorder were reported.

Sample Collection and Analysis

A proximal crown head hair sample was obtained from participating children at the 6.5-year (±8 weeks) study visit.. Hair collection occurred at the same time (n=257) or within 1 year (n=7) of completion of the caregiver's Lifestyle Interview and Substance Use Inventory. Hair was analyzed for methamphetamine, cocaine, cannabinoids, nicotine and their metabolites by the Child Guard™ test of United States Drug Testing Laboratories.

The proximal 3cm hair segment was analyzed for drugs with limits of quantification (LOQ, pg/mg) of 51 for amphetamine, 68 methamphetamine, 58 3,4-methylenedioxymethamphetamine (MDMA), 52 3,4-methylenedioxyamphetamine (MDA), 38 cocaine, 4 benzoylecgonine, 36 norcocaine, 11 cocaethylene, 10 Δ^9-tetrahydrocannabinol (THC), 51 nicotine, and 51 cotinine. For quantification of all analytes, except THC, sample preparation included bead beater pulverization of 20 mg hair followed by overnight methanolic extraction in 1.5mL methanol, sonicating for the first 2h. Analytes were quantified by LCMSMS. For THC analysis, sample preparation involved a sodium hydroxide digest and solid phase extraction. THC was quantified by GC/MS with a LOQ of

10pg/mg. The Child Guard™ test does not include hair washing to improve detection of environmental drug exposure.

Neurobehavioral Disinhibition Measure

Neurobehavioral disinhibition scores were computed from data collected at the 6.5 and 7.5 year visits. Neurobehavioral disinhibition was represented by (a) summary scores from the Children's Memory Scale[30] assessing general memory impairment and learning problems at 6.5 years, (b) Child Behavior Checklist[31] scales assessing attention problems, and rule breaking and aggressive behaviors at 7.5 years, and (c) Conner's Parent Rating Scales[32] assessing cognitive problems/inattention and hyperactivity at 7.5 years. Scales were standardized and averaged creating the neurobehavioral disinhibition scale score (α=0.82), with higher scores indicating more neurobehavioral disinhibition.

Statistical Analysis

Using GraphPad Prism5, chi-square and t-tests evaluated differences between group hair drug concentrations. Hierarchical linear regression models (SPSS 17.0) tested associations between neurobehavioral disinhibition and prenatal, postnatal, and combined prenatal/postnatal substance exposure after controlling for covariates. Postnatal drug exposure was defined exclusively by child hair drug detection results. Model covariates were chosen to account for potential confounding influences on neurobehavioral disinhibition based on previous empirical and conceptual work. Step 1 model covariates were study site, intelligence quotient from the Wechsler Intelligence Scale for Children (WISC)[33] administered at 90 months, low birth weight (<2500g), prenatal care, child sex, maternal education and race, prenatal exposure to alcohol (oz absolute alcohol/day), cannabis and tobacco (average joints or cigarettes/day), maternal Brief Symptom Inventory (BSI)[34] responses averaged through 3 years, and caregiver SES, physical abuse, domestic violence, and neighborhood violence through 6.5 years. PME and postnatal methamphetamine or tobacco exposure were included in Step 2.

Results

Child Hair Toxicology

Methamphetamine, amphetamine, cocaine, benzoylecgonine, THC, cotinine and nicotine were quantified in child hair specimens (Table 1). No hair specimens were positive for MDMA, MDA, norcocaine, or cocaethylene. Prevalence of methamphetamine and/or amphetamine positive hair specimens was significantly greater for PME children than for children without PME (27.1% versus 8.4%, χ^2=15.7, df=1, P<0.0001). Among children without PME, 6 had methamphetamine-positive hair with all 6 negative (<LOQ) for amphetamine. Five children had hair positive for amphetamine but negative for methamphetamine (Table 1). Among PME children, 35 had methamphetamine-positive hair, 10 of which also were positive for amphetamine. In these 10 children, methamphetamine concentrations were 111–14711pg/mg and amphetamine concentrations 56–288pg/mg. In most cases (80%), methamphetamine concentrations exceeded those of amphetamine with ratios ranging from 3.1–73.6. One PME child's hair contained 38282pg/mg amphetamine and no methamphetamine. In hair samples positive for methamphetamine with no

amphetamine among PME children (19%), methamphetamine concentrations ranged from 69–1470pg/mg.

Prevalence of tobacco exposure, as indicated by nicotine and/or cotinine positive hair, was significantly greater for PME children than for children without PME (38.3% versus 25.2%, χ^2=5.3, df=1, *P*=0.02). In vivo, nicotine is oxidized to cotinine primarily by CYP2A13 and CYP2A6.[35] Nicotine was more prevalent than cotinine in hair specimens from both groups (Table 1). Hair from 50 PME children was positive for nicotine and all but 1 (55pg/mg cotinine) of the 24 cotinine-positive specimens also contained nicotine (Table 1). In children without PME, all but 2 (57, 79pg/mg cotinine) of the 12 cotinine-positive specimens also contained nicotine.

There was no difference in positive hair prevalence for cocaine and benzoylecgonine among the PME children (7.5%) and children without PME (4.6%). In the PME group, 6 of the 10 benzoylecgonine-positive hair specimens also contained cocaine. Similar results were seen in the group without PME; 3 specimens contained benzoylecgonine alone, 1 contained cocaine only, and 2 were positive for both cocaine markers. No difference in prevalence was seen for THC-positive hair specimens with THC detected in 7 hair specimens from children without PME and in 3 PME children's hair. In the latter group, 1 specimen was positive for THC alone, and the other 2 were positive for THC along with nicotine and/or cotinine. Three of the 7 THC-positive specimens from children without PME were positive only for this analyte, 4 also were positive for tobacco markers only and 2 also were positive for methamphetamine and tobacco. Significantly more positive hair specimens from PME children contained more than one analyte (69.4%) compared to children without PME (36.5%) (χ^2=11.4, df=1, *P*=0.0008). No significant differences in positive hair concentrations were observed between the two groups (Table 1).

A significantly higher prevalence of concurrent tobacco and methamphetamine positive hair also was seen in PME children (19.5%) compared to children without PME (3.1%) (χ^2=17.8, df=1, *P*<0.0001). Among PME children with methamphetamine and tobacco-positive hair, methamphetamine concentrations ranged from 98–14711pg/mg. Eight specimens were concomitantly positive for amphetamine (56–288pg/mg). One specimen with 2137pg/mg nicotine also contained 38282pg/mg amphetamine and no methamphetamine. Among PME children with nicotine/cotinine negative hair and methamphetamine/amphetamine positive hair, methamphetamine hair concentrations (n=9) ranged from 69–1203pg/mg and (n=2) 121–271pg/mg amphetamine. With a high prevalence of concurrent postnatal tobacco and methamphetamine exposure among PME children, we investigated the effect of postnatal tobacco exposure on child neurobehavioral outcomes in addition to postnatal methamphetamine exposure.

Caregiver Substance Use and Child Amphetamine Medications

Of the 131 children without PME, 129 had complete caregiver substance use information at the time of the child's hair collection; in the PME group (n=133), 127 children had complete caregiver data. In children without PME, it was significantly more likely for the child's biological mother or father to be the primary caregiver at 78 months than in PME children (94.7% versus 49.6%, χ^2=66.3, df=1, P<0.0001). In 48 (36.1%) PME cases, an adopted or

foster parent was the caregiver, and in 13 (9.8%) PME cases, a biological aunt or grandmother was the caregiver.

All primary caregivers of no PME children reported no methamphetamine or amphetamine use in the past year, despite 6 cases of methamphetamine-positive hair (all amphetamine negative) and 5 cases of amphetamine-positive hair (all methamphetamine negative). Three of the 5 children without PME who had amphetamine-positive hair (1265, 3120, and 10,894 pg/mg) were taking amphetamine-containing medications for ADHD, including Adderal (mixed salt preparation of d- and l-amphetamine) and Vyvanse (lysine prodrug of d-amphetamine).

In PME children, no methamphetamine/amphetamine use was reported by primary caregivers in the 11 amphetamine-positive hair cases and in all but one methamphetamine-positive hair case. In only one of 32 methamphetamine-positive hair cases in the PME group, the primary caretaker reported smoking methamphetamine 0.6 days/week; the father also used methamphetamine in this case, although it is unknown how often the child visited or saw the father. In 4 cases in the PME group, the primary caregiver reported using methamphetamine in the past year; however, no methamphetamine was detected in any child's hair. Two PME children were reportedly taking amphetamine-containing medication for ADHD. One child taking Vyvanse had a high amphetamine hair concentration of 38,282pg/mg relative to the other 10 amphetamine-positive hair results in this group (56–288pg/mg amphetamine) and no methamphetamine detected in hair. Another PME child reportedly taking Adderal XR (extended release) had hair negative for amphetamine and methamphetamine; no information is known on when the child starting taking this medication relative to the hair collection.

Tobacco was the most prevalent drug self-reported by primary caregivers in both groups, with a significantly higher prevalence of tobacco use in PME children caregivers as compared to children without PME (47.2% versus 31.8%, χ^2=7.1, df=1, *P*=0.0078). Mean and median (Table 2) hair nicotine and cotinine concentrations were not significantly different among PME and no PME children whose primary caregiver reported tobacco use during the past year (*P* values>0.354). Of the caregivers reporting tobacco use, average cigarette use (Table 2) was significantly higher among children with positive hair as compared to those with negative hair in both groups (*P*=0.0029 no PME, *P*=0.0338 PME children).

There were 6 cocaine/benzoylecgonine-positive hair cases in the no PME group and 9 in the PME group; in all cases, primary caregivers reported no cocaine use. In the remaining cocaine/benzoylecgonine-negative hair in both groups, the primary caregiver reported no cocaine intake except for 1 case in the PME group where the caregiver reported cocaine intake of 1g 0.6 days/week over the last year. In the 2 THC-positive hair cases in the PME group, the primary caregiver reported no cannabis use. In 7 cases of THC-positive hair in the no PME group, 4 primary caregivers reported smoking cannabis with frequency ranging from <0.5–5 joints/day. In 10 other cases in both groups, the primary caregiver reported smoking cannabis (<0.5–30 joints/day); however, the child's hair was THC-negative.

Neurobehavioral Disinhibition Assessment

Secondary grouping of children by postnatal methamphetamine or tobacco exposure allowed investigation into possible differential effects of prenatal versus postnatal drug exposure on child neurobehavioral disinhibition. Demographic data for the 4 categories of methamphetamine exposure: pre- and postnatal methamphetamine exposure, PME with no postnatal exposure, only postnatal methamphetamine exposure, and no prenatal or postnatal exposure, are shown in Table 3. Group differences were seen on some demographic measures (Table 3), for example, mothers of PME children, both with and without postnatal drug exposure, were less likely to have had prenatal care and more likely to drink alcohol, and smoke tobacco and cannabis.

Hierarchical linear regression models evaluated whether postnatal exposure, as identified by hair markers, added additional risk for neurobehavioral disinhibition above the risk related to PME. A significant effect of PME only and combinations of PME with either postnatal methamphetamine or tobacco exposure was seen on child neurobehavioral disinhibition (Table 4); postnatal methamphetamine and tobacco exposures alone were not associated with neurobehavioral disinhibition. The combined effect of prenatal and postnatal methamphetamine was not related to greater neurobehavioral disinhibition than PME alone; regression parameters were not significantly different between children with PME only and those with PME and postnatal methamphetamine exposure. The results for PME and postnatal tobacco exposure were similar. The combined effect of PME and postnatal tobacco exposure was not related to greater neurobehavioral disinhibition than PME alone with no significant differences between relevant regression parameters.

Discussion

Emerging evidence suggests PME may have subtle effects on childhood behavioral and cognitive outcomes.[12, 36] Negative PME consequences include poor behavior, motor and executive function, and problems with inhibitory control, memory, and attention during infancy and childhood.[11, 13–14, 37–39] This collection of adverse behavioral and cognitive effects is described as neurobehavioral disinhibition.[25–26]

These data confirm the association between PME and poor behavioral and executive functions, described as neurobehavioral disinhibition, in 6.5–7.5 year-olds. Neurobehavioral disinhibition in children and adolescents often predicts delinquency, academic difficulties, peer rejection, mental health problems, substance abuse, and juvenile justice system involvement,[25–27] as individuals with these disinhibitory problems follow longitudinal challenges throughout life.

Our data showed no significant effect of postnatal methamphetamine or tobacco exposure alone on neurobehavioral outcomes; the direct impact of environmental drug exposure on child development in children with prenatal drug exposure still remains unclear. Like previous studies,[12] this investigation demonstrates PME is associated with poor child neurobehavior. Methamphetamine-positive hair identifies an unsafe child environment; however, PME identifies children at risk of neurobehavioral disinhibition. If methamphetamine exposure of children is suspected, it is important to investigate both

current child home safety and inquire about maternal drug use in pregnancy. In addition, an association between neurobehavioral disinhibition was also found in PME children with postnatal drug exposures. Additional risk of greater neurobehavioral disinhibition in PME children with postnatal drug exposure was not observed. It is important to consider parental psychosocial characteristics during early childhood as these may result in maladaptive parenting and caregiving, which may lead to greater neurobehavioral disinhibition;[40] however, no group differences were seen between caregiver BSI responses in our study (Table 3).

Hair testing offered a non-invasive means to identify postnatal drug exposure, allowing investigation of postnatal drug exposure effects on child neurobehavioral disinhibition at 6.5 years in a unique population of PME children compared to children without PME. Advantages of hair testing include long windows of detection, allowing drug exposure assessment beyond the drug elimination period, as a 3cm hair segment represents 65–90 days of exposure depending on hair growth rate.[41] Hair testing in children focuses on external contamination and is enhanced by eliminating hair washes, unlike for adult hair analysis that includes washing to remove external contamination. Documenting drug exposure in children's hair is an indicator that families need services or that home removal may be necessary. Child hair testing can detect accidental ingestion as well as passive exposure. Drug use even in at-risk populations does not usually occur until early adolescence, most often at ages 10–12.[36]

In this study, methamphetamine-positive hair was significantly more prevalent among PME children than children without PME. Hair methamphetamine concentrations in PME children were lower than those removed from clandestine methamphetamine laboratories in New Zealand (n=52, mean 7000pg/mg);[20] however, our study documented similar hair methamphetamine/amphetamine ratios.[20] Mean adult methamphetamine and amphetamine hair concentrations after 40mg oral methamphetamine administration were 1780 and 200pg/mg respectively;[42] mean hair concentrations from this study's PME children were similar (1287pg/mg methamphetamine and 141pg/mg amphetamine, excluding outlier 38282pg/mg amphetamine). Similar mean concentrations may indicate children in our study ingested methamphetamine in the home, or had repetitive exposures.

Amphetamine concentrations in methamphetamine-negative hair in our study were elevated compared to previous cohorts, likely indicating the impact of child amphetamine ADHD medication use. Four of the five children taking amphetamine-containing medications (Adderal and/or Vyvanse) in this study had amphetamine-positive, methamphetamine-negative hair. Another PME child reportedly taking Adderal XR (extended release amphetamine) had methamphetamine- and amphetamine-negative hair. However, it is unknown when this child started taking the amphetamine-containing medication relative to the timing of hair collection and how compliant the child was with his or her medication. Our results demonstrate that knowing child medication history is important for improved hair result interpretation. These data on child hair amphetamine concentrations with reported amphetamine medication history may aid clinical differentiation of methamphetamine and amphetamine exposures.

Methamphetamine-positive hair indicated postnatal exposure to methamphetamine; however amphetamine-positive hair may have reflected amphetamine medication ingestion, as well as possible methamphetamine exposure. In both groups of children, most (4/6) children with amphetamine-positive, methamphetamine-negative hair were taking amphetamine-containing ADHD medication. The other 2 children with amphetamine-positive, methamphetamine-negative hair may have received amphetamine medication exposure not reported by the caregiver. Other children with methamphetamine- and amphetamine-positive hair, either had hair positive for both methamphetamine and amphetamine, or methamphetamine alone, suggesting that positive hair findings reflected methamphetamine exposure.

Nicotine- or cotinine-positive hair indicated postnatal tobacco exposure in this study. Nicotine was detected in all but 3 hair specimens positive for tobacco markers. Presence of nicotine alone may indicate exposure of hair to tobacco smoke containing nicotine where as presence of cotinine alone, or in combination with nicotine, suggests possible inhalation of tobacco smoke by the child as metabolic activity is required for cotinine generation.

Cannabinoid hair analysis is particularly difficult because of lower binding to hair melanin compared to more basic drugs like cocaine and methamphetamine.[43–44] In adults, 11-nor-9-carboxy-THC (THCCOOH) analysis rules out passive environmental contamination as THCCOOH is formed only *in vivo* after cannabis ingestion.[43] THCCOOH in children's hair may have identified more potentially exposed children, if the children ingested cannabis; however, hair THC analysis in children is sufficient to identify exposure and/or ingestion.

This study is unique, as self-reported caregiver substance use information was collected simultaneously with children's hair samples in 97.3% of cases, and within 1 year in 2.7%. Agreement between caregiver-reported methamphetamine intake and methamphetamine hair results among both groups of children was poor, as only one child with positive methamphetamine in hair had a positive caregiver methamphetamine self-report. Caregiver illicit drug use using the Lifestyle Interview and Substance Abuse Inventory[29] was underreported (as indicated by child hair test discrepancies) despite assurance of confidentiality and long staff participant relationships. These findings support continued hair testing in these children as positive hair findings identified more drug exposure than caregiver self-report. In our study, child hair results were the determining factor in documenting postnatal exposure. Agreement between caregiver reported tobacco use and hair results was better than for methamphetamine. Sensitivity and specificity results for the tobacco hair test were 57.4% and 84.6%, respectively, with caregiver self-report as the reference method. Methamphetamine hair test results showed 20.0% sensitivity and 85.3% specificity; however, when evaluating hair amphetamine/methamphetamine results and including child medication history with caregiver self-report, sensitivity improved to 50.0% and specificity to 84.1%. Although limitations of self-report are well known, postnatal self-report measures of maternal cocaine use were as effective as antenatal measures in predicting neurobehavioral child outcomes.[45] Possible reasons for child hair and caregiver report discrepancies include underreporting, a survey questioning period unreflective of the drug exposure period represented by hair, and drug exposure from other family members or household visitors. When the caregiver self-reported drug use and the child's hair was

negative, additional information of how the caregiver uses drugs (inside or outside the child's home) may allow for further interpretation.

Limitations of this study include lack of child hair color or melanin content information, and the single time point evaluation of postnatal drug exposure. Challenges to child hair result interpretation include knowledge of hair color or hair treatment. Methamphetamine incorporation into adult hair after controlled oral dosing showed a dose-concentration relationship mediated by hair melanin content.[42] Information on hair color and melanin may have improved interpretation of hair toxicology findings. Hair analysis of a 3cm segment at 6.5 years provided postnatal drug exposure identification during the past 3 months; however, no interpretation can be made regarding drug exposure from infancy to this time point. Hair collection and analysis at 6.5 years of age provided a means to evaluate and compare effects of PME with drug exposure at this age.

Conclusion

This study demonstrates higher prevalence of postnatal methamphetamine, tobacco and concurrent methamphetamine and tobacco exposure, as assessed with hair testing, in PME children compared to children without PME. Agreement between caregiver reported illicit drug use and child hair results was poor. There was better agreement between child hair results and caregiver reports for tobacco smoking. Child hair drug testing is a non-invasive means to assess environmental drug exposure. Risk for neurobehavioral disinhibition, as determined by poor behavior and executive function, was demonstrated in PME children and PME children with environmental postnatal exposures. These data confirm findings of other studies,[12, 25, 39] suggesting that PME prevention may lead to reduced risk of neurobehavioral disinhibition. Postnatal environmental drug exposure, as indicated by positive hair test, did not add additional risk of neurobehavioral disinhibition, advocating prevention efforts should focus on prenatal drug exposures. Additional research is needed to understand how methamphetamine cessation or reduction during pregnancy improves child health and development. When prevention efforts are unsuccessful, early methamphetamine exposure identification is critical to providing interventions that improve child development and mother and child well-being.

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Table 1

Median (range) positive hair drug concentrations from 6.5 year old children with and without prenatal methamphetamine exposure (PME)

	Hair concentrations (pg/mg)				
	No PME (n=131)		PME (n=133)		
	N	Median (Range)	N	Median (Range)	*P* values[a]
Methamphetamine	6	521 (76 – 930)	35	369 (69 – 14711)	0.6448
Amphetamine	5	1265 (74 – 553,1265 – 10894[b])	11	121 (56 – 288, 38282[c])	0.0893
MDMA	0	<LOQ	0	<LOQ	
MDA	0	<LOQ	0	<LOQ	
Cocaine	3	102 (74 – 195)	6	62 (39 – 315)	0.5476
Benzoylecgonine	5	27 (9 – 203)	10	13 (6 – 72)	0.2442
Norcocaine	0	<LOQ	0	<LOQ	
Cocaethylene	0	<LOQ	0	<LOQ	
THC	7	55 (11 – 333)	3	220 (47 – 737)	0.3605
Cotinine	12	121 (57 – 244)	24	138 (51 – 690)	0.5201
Nicotine	31	396 (64 – 5949)	50	686 (52 – 56859)	0.3818

[a] Medians compared with non-parametric Mann-Whitney t-tests

[b] Children with 1265, 3120 and 10894pg/mg amphetamine were taking amphetamine containing medication (Vyvanse or Adderal) for ADHD. Included in median calculation.

[c] Child with 38282pg/mg amphetamine was taking amphetamine-containing medication (Vyvanse) for ADHD. Included in median calculation.

Table 2

Self-reported tobacco use by primary caregiver and child hair toxicology results

No PME				
Primary Caregiver's Reported* Tobacco Use (n=129)	Child Hair Tobacco Result	Nicotine n, median (range)	Cotinine n, median (range)	Average Cigarettes/Day Reported in last year (mean ± SD, range)
Yes (n=40, 31%)	Positive n=20	n=20, 681 (98–5297)	n=7, 140 (60–244)	10.6 ± 7.0 (0.09–30)
	Negative n=20			5.2 ± 4.3 (0.01–10)
No (n=89, 69%)	Positive n=13	n=11, 224 (64–5949)	n=5, 79 (57–218)	
	Negative n=76			
PME				
Primary Caregiver's Reported* Tobacco Use (n=127)	Child Hair Tobacco Result	Nicotine n, median (range)	Cotinine n, median (range)	Average Cigarettes/Day Reported in last year (mean ± SD, range)
Yes (n=60, 47.2%)	Positive n=37	n=37, 681 (66–56859)	n=16, 181 (51–690)	11.5 ± 10.6 (0.01–50)
	Negative n=23			6.6 ± 6.6 (0.04–20)
No (n=67, 52.8%)	Positive n=11	n=10, 274 (52–13325)	n=7, 104 (55–472)	
	Negative n=56			

* reported use during last year

Table 3

Demographics of prenatal and postnatal methamphetamine (MAMP) exposure (PME) groups

Demographic*	PME/ Postnatal MAMP Exposure (n=35)	PME/No Postnatal MAMP Exposure (n=98)	No PME/ Postnatal MAMP Exposure (n=6)	No PME/No postnatal MAMP Exposure (n=125)
Male	20 (57.1%)	46 (46.9%)	5 (83.3%)	56 (44.8%)
Low birth weight ≤2500 g	4 (11.4%)	13 (13.3%)	1 (16.7%)	12 (9.6 %)
Mother's race-minority	18 (51.4%)	64 (65.3%)	3 (50.0%)	75 (60%)
Prenatal care[1,2]	30 (85.7%)	90 (91.8%)	6 (100%)	125 (100%)
Maternal education < high school[2]	15 (42.9%)	46 (46.9%)	3 (50%)	42 (33.9%)
Average number of cigarettes/day across pregnancy[1,2,5]	7.0 (6.3)	7.0 (6.3)	1.0 (2.0)	1.2 (3.9)
Average oz. absolute alcohol/day across pregnancy[1,2]	0.09 (0.42)	0.08 (0.25)	-	0.005 (0.02)
Average number of cannabis joints/day across pregnancy[2]	0.04 (0.11)	0.08 (0.25)	-	0.02 (0.11)
Average Caregiver SES[1,2,4]	27.7 (6.3)	31.9 (9.2)	29.9 (4.4)	34.7 (9.3)
Community violence	1.6 (1.5)	1.5 (1.5)	1.2 (1.6)	1.7 (1.6)
Child WISC composite score	95.6 (9.4)	94.7 (12.0)	100.0 (14.4)	97.0 (13.3)
Caregiver abuse[2]	1 (2.9%)	12 (12.2%)	1 (16.7%)	6 (4.8%)
Caregiver psychopathology (BSI)	0.53 (0.46)	0.45 (0.41)	0.17 (0.12)	0.50 (0.41)

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

[1]PME/Postnatal MAMP vs. No PME/No Postnatal MAMP (P<0.05)

[2]PME/No Postnatal MAMP vs. No PME/No Postnatal MAMP (P<0.05)

[3]No PME/Postnatal MAMP vs. No PME/No Postnatal MAMP (P<0.05)

[4]PME/Postnatal MAMP vs. PME/No Postnatal MAMP (P<0.05)

[5]PME/Postnatal MAMP vs. No PME/Postnatal MAMP (P<0.05)

[6]PME/No Postnatal MAMP vs. No PME/Postnatal MAMP (P<0.05)

Table 4

Effects of prenatal methamphetamine (PME) and postnatal drug exposure on child neurobehavioral disinhibition at 6.5 years

PME and Postnatal Methamphetamine Exposure			**PME and Postnatal Tobacco Exposure**		
	standardized β	***P***		**standardized β**	***P***
PME Only	0.202[a]	0.022	PME Only	0.227[b]	0.003
Postnatal Methamphetamine Only	−0.052	0.391	Postnatal Tobacco Exposure Only	0.111	0.115
PME and Postnatal Methamphetamine	0.152[a]	0.025	PME and Postnatal Tobacco Exposure	0.273[b]	0.001

Note: β coefficients observed when accounting for model covariates listed in the statistical analysis section.

[a] No statistical difference between regression parameters for PME only (0.202) and PME plus postnatal methamphetamine exposure (0.152), *P*=0.876.

[b] No statistical difference between regression parameters for PME only (0.227) and PME plus postnatal tobacco exposure (0.273), *P*=0.286.