# Cortisol Reactivity in Two-Year-Old Children Prenatally Exposed to Methamphetamine

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**ABSTRACT. Objective:** Until now, the functioning of the hypothalamic–pituitary–adrenal (HPA) axis in children with prenatal methamphetamine exposure (PME) had been unexamined. Previous research indicates that prenatal exposure to stimulant drugs is associated with dose-response alterations in neural growth and connectivity and consequent neurobehavioral deficits. In addition, children of drug-using parents are at an increased risk for exposure to chronic postnatal stress. In this preliminary study, we examined the associations of PME and postnatal environmental stress with cortisol stress reactivity in children with PME. **Method:** Participants were 2-year-old children ($N$ = 123; 55.3% male) with PME from a multicenter longitudinal Infant, Development, Environment, and Lifestyle Study. Saliva samples were obtained before and after a stress-inducing separation task. Hierarchical multiple regression analyses examined prenatal drug exposure, methodological and postnatal stress covariates, and interactions between levels of PME and postnatal stress. **Results:** Mild to moderate potential for child physical abuse moderated increased cortisol reactivity in high exposed children with PME. Blunted cortisol reactivity was associated with caregiver's postnatal alcohol use, child's behavioral dysregulation, and the interaction between higher levels of PME and caregiver's psychopathology. **Conclusions:** Consistent with the known effects of stimulant drugs and chronically stressful environments on the HPA axis and, thus, the toxic stress and allostatic load phenomena, our results imply that elevated PME may be associated with alterations in the programming of the HPA axis reflecting hyperactivity, which under significant and chronic environmental stress then may become hypoactive. (*J. Stud. Alcohol Drugs, 74,* 447–451, 2013)

METHAMPHETAMINE USE IS A SERIOUS problem in the United States, with an estimated 353,000 users ages 12 years and older in 2010 (Substance Abuse and Mental Health Services Administration, 2011). Rates of methamphetamine use among pregnant women have been reported to be as high as 5.2% (Arria et al., 2006). Although the deleterious effects of methamphetamine on the female adult user are well documented (Cruickshank and Dyer, 2009), less is known about the effects on a developing fetus and child.

Children with prenatal methamphetamine exposure (PME) are at an increased risk for alterations in neural growth and connectivity and consequent neurobehavioral deficits (Salisbury et al., 2009). Unlike cocaine, another stimulant of the sympathetic nervous system, methamphetamine has a greater neurotoxic effect because of its longer half-life and direct transport into the cell (Sowell et al., 2010). Neuroimaging studies of children with PME indicate volume reduction in cortical and subcortical brain structures (Sowell et al., 2010). In addition, adverse dose-response neurobehavioral effects, suggestive of alterations in the functioning of the hypothalamic–pituitary–adrenal (HPA) axis, have been reported among children with PME (Salisbury et al., 2009). Specifically, in the first 5 days of life PME is linked to decreased arousal, increased stress, lethargy, and poor movement quality (Smith et al., 2008); long-term neurobehavioral deficits include poorer motor performance among

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most heavily exposed 3 year olds (Smith et al., 2011) and poorer visual tasks performance, delayed verbal memory, and lower full-scale intelligence quotient scores in 7- and 15-year-olds (Roussotte et al., 2010).

In addition to PME, these children are at a greater risk for adverse early life events, including exposure to physical violence, parental psychopathology, and ongoing parental drug use (Brown and Hohman, 2006). Drug use among primary caregivers is often associated with change in custody, violent behaviors, abuse and neglect, and substance dependence (Conners et al., 2003; Derauf et al., 2007; Zweben et al., 2004). Thus, the chronically stressful postnatal environment may exacerbate the adverse effects of PME on neural development and neuroendocrine mechanisms.

To date, the HPA-axis functioning in children with PME has been unexamined, whereas previous research is inconsistent regarding other stimulants (e.g., cocaine). Specifically, increased cortisol reactivity has been observed in children (Eiden et al., 2009) and adolescents (Chaplin et al., 2010) prenatally exposed to cocaine, an association influenced by caregiver instability and male gender. Decreased cortisol reactivity (blunting), conversely, has been found in young adolescents exposed to cocaine (Lester et al., 2010), a relationship moderated by exposure to domestic violence. Similarly, stressful early environments have been implicated in both increased and decreased cortisol reactivity, with chronicity and severity implicated as moderators (De Bellis, 2005; Heim et al., 2000). These findings support the hypothesis that although higher rates of stress may initially result in an overactive HPA axis, underactivation may be a long-term consequence of chronic and severe exposure (McEwen, 1998). Therefore, objectives of the present study were to (a) examine the relationship between PME and cortisol reactivity in children and (b) assess whether PME and significant, chronic postnatal stress in young children are associated with blunted cortisol responses.

## Method

### *Participants*

The sample came from a longitudinal prospective multisite study examining effects of PME on child development. Detailed procedures for the Infant Development, Environment, and Lifestyle (IDEAL) study are described elsewhere (Smith et al., 2006). PME was identified at birth by mother's self-report and/or gas chromatography/mass spectrometry confirmation of amphetamines and metabolites in infant's meconium. Exclusion criteria were (a) prenatal exposure to opiates, lysergic acid diethylamide, phencyclidine, hallucinogens, or cocaine or (b) chromosomal abnormality associated with mental or neurological deficiency. The study had approval from respective institutional review boards at each location (California, Hawaii, Iowa, and Oklahoma). A National Institute on Drug Abuse Certificate of Confidentiality was obtained for the project to assure confidentiality of information regarding drug use; however, evidence of child abuse or neglect was reportable. All caregivers provided informed consent. The initial sample included 204 children with PME, of whom 154 were seen at the 2-year follow-up. A total of 140 children provided saliva samples. Insufficient saliva quantity or biologically implausible cortisol values were found in 17 children, thus yielding a final sample of 123 children with PME. No significant differences were found on baseline caregiver and child characteristics between the examined and unexamined samples.

### *Procedure*

A modified Lifestyle Interview (Lester et al., 2002) and the Substance Use Inventory (Della Grotta et al., 2010) provided demographic and detailed drug use information during pregnancy and at 24-month follow-up. The level of PME was calculated per mother's report as the number of days of methamphetamine use during pregnancy, ranging from once a month to almost daily. Prenatal exposure to marijuana, alcohol, and tobacco were calculated using the same procedure. In this study, indicators of chronic stress that had been previously associated with drug-using caregivers (Brown and Hohman, 2006) were ongoing postnatal substance use, psychopathology, and potential for physical abuse. Postnatal substance use was defined as any use of methamphetamine, marijuana, or alcohol. Psychiatric symptoms of the primary caregiver were evaluated with the Brief Symptom Inventory (Derogatis, 1993). Psychopathology was denoted by a T score of 63 or greater on the Global Severity Index or on any two primary dimensions. The Child Abuse Potential Inventory (Milner, 1986) assessed the potential for physical abuse toward the child.

Cortisol stress reactivity was assessed based on a separation task administered at a 2-year clinic visit using a modified version of a well-established methodology known to be stress inducing for children (Gunnar et al., 2009; Jacobson et al., 1999). The baseline saliva sample was collected, and the child's emotional state was rated (5-point scale: *calm* to *very highly agitated*) approximately 30 minutes after arrival at the clinic, on the completion of the Early Social Communication Scales (ESCS; Mundy et al., 1996). The ESCS is a 20-minute interaction task between the examiner and the child, coded for joint attention (e.g., eye contact), social interactions (e.g., initiating turn-taking), and behavioral regulation (e.g., responding to behavioral requests). Failure to respond to behavioral requests was used to measure behavioral dysregulation. During the following 12 minutes, the caregiver and the child engaged in structured (Johnson et al., 2002) and nonstructured play. Next, a prompt was given to the caregiver and the examiner to leave the room. The child was left alone in the room for a maximum of 2 minutes, followed

by 1 minute with the examiner only (no interaction with the child), after which the caregiver returned. If the child became very upset, the caregiver returned earlier. Twenty minutes after the separation, the second saliva sample (stress response) was collected.

Saliva samples were collected for 1 minute (0.5 ml/sample) using two polyurethane foam collectors designed specifically to collect oral fluid specimens, stored at -20 °C, and shipped on dry ice to Salimetrics, LLC (State College, PA). Samples were analyzed using a high-sensitivity salivary cortisol enzyme immunoassay.

### *Statistical analysis*

Raw cortisol values (μg/dl) were positively skewed and thus normalized using a natural log transformation. Outliers 3 *SD* or more from the mean were Winsorized by replacing their value with the nearest value less than 3 *SD* from the mean. Baseline and stress response samples were analyzed twice to produce mean baseline and response values, respectively. Next, mean stress response values were subtracted from the mean baseline values to produce the change in cortisol values (reactivity). Hierarchical multiple regression was used to examine predictors of cortisol reactivity. In addition to level of PME, the base model included the level of prenatal exposure to alcohol, marijuana, or tobacco. Also entered in the base model were methodological covariates (child's sex, birth weight, time since last meal, baseline saliva collection time, baseline saliva collection emotional state, and behavioral dysregulation) and measures of postnatal stress (caregiver's postnatal methamphetamine, alcohol, or marijuana use; psychopathology; and potential for physical abuse). Ninety-one percent of children were securely attached, deeming attachment a redundant covariate. Differences in the associations between the level of PME and cortisol reactivity by postnatal stress were examined in the second model with two interaction terms, PME × Psychopathology and PME × Potential for Physical Abuse.

Table 1. Demographic characteristics and cortisol samples values ($n$ = 123)

| Variable | $n$ (%) or $M$ ($SD$) |
|---|---|
| Child | |
| Male | 68 (55.30%) |
| Gestational age, weeks | 38.44 (2.28) |
| Birth weight, g | 3,228.71 (615.49) |
| Head circumference, cm | 33.75 (1.79) |
| Birth length, cm | 49.71 (3.59) |
| Baseline emotional state[a] | 1.30 (0.79) |
| Behavioral dysregulation[b] | 2.62 (4.53) |
| Caregiver | |
| Race, Black | 6 (4.90%) |
| Single | 68 (55.30%) |
| Socioeconomic status | 24.23 (9.35) |
| Prenatal MA use, days per week | 1.74 (1.81) |
| Prenatal alcohol use | 47 (38.20%) |
| Prenatal marijuana use | 43 (35.00%) |
| Prenatal tobacco use | 95 (77.20%) |
| Postnatal MA use | 19 (15.40%) |
| Postnatal alcohol use | 58 (47.20%) |
| Postnatal marijuana use | 13 (10.60%) |
| Psychopathology[c] | 41 (36.00%) |
| Caregiver physical abuse potential[d] | 127.76 (94.46) |
| Cortisol | |
| Baseline[e] | 0.18 (0.21) |
| Reactivity[e] | 0.13 (0.11) |
| Mean change[e] | -0.05 (0.15) |
| Increased response | 39 (31.70%) |
| Blunted response | 84 (68.30%) |

*Notes:* MA = methamphetamine. [a]Evaluated on a 5-point scale: *calm* (1) to *very highly agitated* (5). [b]Assessed by the Early Social Communication Scales as the number of child's failures in responding to behavioral requests. [c]Evaluated with the Brief Symptom Inventory; psychopathology denoted by a $T$ score ≥ 63 on the Global Severity Index, or on any two primary dimensions. [d]Assessed by Child Abuse Potential Inventory. The score indicates mild to moderate potential for physical abuse. [e]Cortisol levels in μg/dl. The analyzed cortisol data have been log transformed.

## Results

Descriptive and demographic data are presented in Table 1. Thirty-two percent of children exhibited increased cortisol reactivity after separation from their caregiver (stress response values greater than baseline), whereas 68% showed blunted reactivity (stress response values equal to or lower than baseline). The final hierarchical multiple regression model, containing the interaction terms (PME × Psychopathology and PME × Potential for Physical Abuse), showed a significant improvement over the base model ($\Delta R^2$ = .05, $p$ < .05) that included main effects of postnatal alcohol use (β = -.32), $t(88)$ = -3.08, $p$ < .01, and behavioral dysregulation (β = -.44), $t(88)$ = -3.92, $p$ < .001. The final model accounted for 23% of the variance (adjusted $R^2$) in change in cortisol reactivity, $F(17, 103)$ = 2.79, $p$ < .01. Significant predictors of increased cortisol reactivity were higher levels of PME (β = .28), $t(86)$ = 2.01, $p$ < .05, greater potential for physical abuse (β = .31), $t(86)$ = 2.49, $p$ < .05, and the interaction of PME × Potential for Physical Abuse (β = .29), $t(86)$ = 2.40, $p$ < .05. Children with higher levels of PME whose caregivers reported greater potential for physical abuse showed increased cortisol reactivity after separation from the caregiver. Postnatal alcohol use (β = -.36), $t(86)$ = -3.47, $p$ < .01, behavioral dysregulation (β = -.47), $t(86)$ = - 4.31, $p$ < .001, and the PME × Psychopathology interaction (β = -.35), $t(86)$ = -2.43, $p$ < .05, predicted blunted cortisol reactivity in children during separation from the caregiver. Children with higher levels of PME living with caregivers with psychopathology showed blunted cortisol reactivity after separation.

## Discussion

This preliminary study is novel in that it reveals associations between PME, postnatal stress, and HPA-axis functioning in young children. Furthermore, it provides first evidence

of cortisol blunting in young children exposed to stimulants prenatally and significant stress postnatally.

Our analyses show both increased and blunted cortisol responses to a stress-inducing task in 2-year-old children with PME. Thirty-eight percent of the children exhibited an increased response, associated with higher levels of exposure and greater potential for abuse. The remaining children showed a blunted response, linked to behavioral dysregulation, caregiver's alcohol use, and higher levels of exposure together with postnatal environment marked by caregiver's psychopathology.

The findings first support the hypothesis that PME may relate to alterations in the function of the HPA axis (Salisbury et al., 2009). Because methamphetamine is a stimulant of the sympathetic nervous system, prenatal exposure can cause increased synaptic concentrations of dopamine, serotonin, and norepinephrine. The increase occurs because of the direct release of these neurotransmitters into synapses, blockage of monoamine reuptake mechanisms, and inhibition of monoamine oxidase. Inhibition of monoamine oxidase caused by PME may further lead to an increase in synaptic catecholamine levels. In addition, methamphetamine's vasoconstrictive effects may result in decreased uteroplacental blood flow and fetal hypoxia. Last, PME causes a downregulation of the placental norepinephrine transporter and 11β-hydroxysteroid dehydrogenase-2, which protect the fetus against the excess catecholamines and glucocorticoids. Consequent cortisol overexposure can adversely affect the programming of the HPA axis (Salisbury et al., 2009). Therefore, the observed increased cortisol reactivity to a stressful task among children in this study is in line with the suggested effects PME has on the fetus's HPA-axis programming. We also report that abuse potential moderated increased reactivity in children with PME. Although physical abuse may be a significant postnatal stressor, the data in our sample were positively skewed, suggesting potential for mild to moderate physical child abuse (Milner, 1986). Mild abuse is characterized by transitory and situational physical force not representative of the typical parenting style and lacking any injury. Moderate abuse is marked by transitory and situational physical force that is nonaccidental in its nature and results in minimal, nonimpairing injury for the child. Thus, elevations seen in our sample indicate instances in which minimal physical force was used, with no resulting injury or impairment, thus constituting a significant, but not a severe and chronic, stressor.

Second, the results indicate that postnatal exposure to chronic and severe stress was associated with cortisol blunting in young children exposed to substances, findings only observed to date in 10- (Fisher et al., 2012) and 11-year-old children (Lester et al., 2010). In this study, the caregiver's psychopathology moderated the relationship between elevated PME and cortisol reactivity. Research suggests that children of caregivers with psychopathology may be exposed to maltreatment and neglect, including emotional and physical abuse, domestic violence and aggression, and rejection (Famularo et al., 1992; Sidebotham et al., 2001). Similar environmental stressors are reported in children of alcohol-misusing caregivers (Dube et al., 2001), a significant predictor of cortisol blunting in children with PME in this study. Last, a significant correlate of cortisol blunting was behavioral dysregulation, characterized by child's failure to respond to the examiner and communicate his or her needs and wants (Mundy et al., 1996). In our sample, factors such as PME and caregiver's psychopathology and ongoing drug use may be exerting a strong, frequent, and prolonged activation of the HPA axis. Referred to as toxic stress by Shonkoff and colleagues (2009), this pattern of activation may adversely affect brain architecture and HPA-axis programming. Specifically, repeated activation of the HPA axis may result in the body's inability to recover from the physiological response (increased reactivity). Over time, however, the HPA axis may become underactive in an attempt to adapt to conditions of chronic stress, manifested by unresponsiveness to novel stressful situations (blunted reactivity). This phenomenon has been referred to as the allostatic load, or the toll the body pays when adapting to sustained psychosocial or physical stress (McEwen, 1998). Consistent with known effects of stimulant drugs on the HPA axis (Salisbury et al., 2009) and the toxic-stress (Shonkoff et al., 2009) and allostatic-load (McEwen, 1998) theories, our results imply that elevated PME may be associated with alterations in the programming of the HPA axis reflecting hyperactivity, which under significant and chronic environmental stress then may become hypoactive.

A limitation of this study is that polysubstance use is considerably common in drug-using populations, including our sample. Although we controlled for prenatal use of alcohol, marijuana, and tobacco and found unique effects of PME, future research warrants controlled studies of mono- vs. polysubstance exposure. Second, we controlled for child's sex, birth weight, time since last meal, cortisol collection time, and baseline emotional state but did not account for potential effects of steroid medication and food or beverage consumption on cortisol reactivity. Last, examination of diurnal patterns of cortisol secretion and comparisons with nonexposed groups would further delineate the impact of PME and postnatal stress on the HPA-axis functioning.

Nevertheless, the implications of these findings, particularly the 68% rate of cortisol blunting found in our sample, are potentially serious and long lasting. Children exposed to significant postnatal stress showing similar cortisol blunting are at a higher risk for development of depression, posttraumatic stress disorder, attention-deficit/hyperactivity disorder, substance use, aggression, and antisocial behaviors (Heim and Nemeroff, 2001; Gunnar and Vazquez, 2001), as well as bodily disorders, including autoimmune disorders, fibromyalgia, and asthma (Heim et al., 2000).

## References


Arria, A. M., Derauf, C., LaGasse, L. L., Grant, P., Shah, R., Smith, L., . . . Lester, B. (2006). Methamphetamine and other substance use during pregnancy: Preliminary estimates from the Infant Development, Environment, and Lifestyle (IDEAL) study. *Maternal and Child Health Journal, 10,* 293–302.

Brown, J. A., & Hohman, M. (2006). The impact of methamphetamine use on parenting. *Journal of Social Work Practice in the Addictions, 6,* 63–88.

Chaplin, T. M., Freiburger, M. B., Mayes, L. C., & Sinha, R. (2010). Prenatal cocaine exposure, gender, and adolescent stress response: A prospective longitudinal study. *Neurotoxicology and Teratology, 32,* 595–604.

Conners, N. A., Bradley, R. H., Mansell, L. W., Liu, J. Y., Roberts, T. J., Burgdorf, K., & Herrell, J. M. (2003). Children of mothers with serious substance abuse problems: An accumulation of risks. *American Journal of Drug and Alcohol Abuse, 29,* 743–758.

Cruickshank, C. C., & Dyer, K. R. (2009). A review of the clinical pharmacology of methamphetamine. *Addiction, 104,* 1085–1099.

De Bellis, M. D. (2005). The psychobiology of neglect. *Child Maltreatment, 10,* 150–172.

Della Grotta, S., LaGasse, L. L., Arria, A. M., Derauf, C., Grant, P., Smith, L. M., . . . Lester, B. M. (2010). Patterns of methamphetamine use during pregnancy: Results from the Infant Development, Environment, and Lifestyle (IDEAL) Study. *Maternal and Child Health Journal, 14,* 519–527.

Derauf, C., LaGasse, L. L., Smith, L. M., Grant, P., Shah, R., Arria, A., . . . Lester, B. M. (2007). Demographic and psychosocial characteristics of mothers using methamphetamine during pregnancy: Preliminary results of the Infant Development, Environment, and Lifestyle study (IDEAL). *American Journal of Drug and Alcohol Abuse, 33,* 281–289.

Derogatis, L. R. (1993). *Brief Symptom Inventory: Administration, scoring and procedures manual* (4th ed.). Minneapolis, MN: NCS, Pearson.

Dube, S. R., Anda, R. F., Felitti, V. J., Croft, J. B., Edwards, V. J., & Giles, W. H. (2001). Growing up with parental alcohol abuse: Exposure to childhood abuse, neglect, and household dysfunction. *Child Abuse & Neglect, 25,* 1627–1640.

Eiden, R. D., Veira, Y., & Granger, D. A. (2009). Prenatal cocaine exposure and infant cortisol reactivity. *Child Development, 80,* 528–543.

Famularo, R., Kinscherff, R., & Fenton, T. (1992). Psychiatric diagnoses of abusive mothers: A preliminary report. *Journal of Nervous and Mental Disease, 180,* 658–661.

Fisher, P. A., Kim, H. K., Bruce, J., & Pears, K. C. (2012). Cumulative effects of prenatal substance exposure and early adversity on foster children's HPA-axis reactivity during a psychosocial stressor. *International Journal of Behavioral Development, 36,* 29–35.

Gunnar, M. R., Talge, N. M., & Herrera, A. (2009). Stressor paradigms in developmental studies: What does and does not work to produce mean increases in salivary cortisol. *Psychoneuroendocrinology, 34,* 953–967.

Gunnar, M. R., & Vazquez, D. M. (2001). Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. *Development and Psychopathology, 13,* 515–538.

Heim, C., Ehlert, U., & Hellhammer, D. H. (2000). The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology, 25,* 1–35.

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry, 49,* 1023–1039.

Jacobson, S. W., Bihun, J. T., & Chiodo, L. M. (1999). Effects of prenatal alcohol and cocaine exposure on infant cortisol levels. *Development and Psychopathology, 11,* 195–208.

Johnson, A. L., Morrow, C. E., Accornero, V. H., Xue, L., Anthony, J. C., & Bandstra, E. S. (2002). Maternal cocaine use: Estimated effects on mother-child play interactions in the preschool period. *Journal of Developmental & Behavioral Pediatrics, 23,* 191–202.

Lester, B. M., LaGasse, L. L., Shankaran, S., Bada, H. S., Bauer, C. R., Lin, R., . . . Higgins, R. (2010). Prenatal cocaine exposure related to cortisol stress reactivity in 11-year-old children. *Journal of Pediatrics, 157,* 288–295.

Lester, B. M., Tronick, E. Z., LaGasse, L., Seifer, R., Bauer, C. R., Shankaran, S., . . . Maza, P. L. (2002). The maternal lifestyle study: Effects of substance exposure during pregnancy on neurodevelopmental outcome in 1-month-old infants. *Pediatrics, 110,* 1182–1192.

McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences, 840,* 33–44.

Milner, J. (1986). *The child abuse potential inventory manual.* DeKalb, IL: Psytec.

Mundy, P., Hogan, A., & Doehring, P. (1996). *A preliminary manual for the abridged Early Social Communication Scales (ESCS).* Unpublished manuscript, University of Miami, Coral Gables, Florida.

Roussotte, F., Soderberg, L., & Sowell, E. (2010). Structural, metabolic, and functional brain abnormalities as a result of prenatal exposure to drugs of abuse: Evidence from neuroimaging. *Neuropsychology Review, 20,* 376–397.

Salisbury, A. L., Ponder, K. L., Padbury, J. F., & Lester, B. M. (2009). Fetal effects of psychoactive drugs. *Clinics in Perinatology, 36,* 595–619.

Shonkoff, J. P., Boyce, W. T., & McEwen, B. S. (2009). Neuroscience, molecular biology, and the childhood roots of health disparities: Building a new framework for health promotion and disease prevention. *Journal of the American Medical Association, 301,* 2252–2259.

Sidebotham, P., & Golding, J., & the ALSPAC Study Team. (2001). Child maltreatment in the "children of the nineties": A longitudinal study of parental risk factors. *Child Abuse & Neglect, 25,* 1177–1200.

Smith, L. M., LaGasse, L. L., Derauf, C., Grant, P., Shah, R., Arria, A., . . . Lester, B. M. (2006). The Infant Development, Environment, and Lifestyle Study: Effects of prenatal methamphetamine exposure, polydrug exposure, and poverty on intrauterine growth. *Pediatrics, 118,* 1149–1156.

Smith, L. M., LaGasse, L. L., Derauf, C., Grant, P., Shah, R., Arria, A., . . . Lester, B. M. (2008). Prenatal methamphetamine use and neonatal neurobehavioral outcome. *Neurotoxicology and Teratology, 30,* 20–28.

Smith, L. M., LaGasse, L. L., Derauf, C., Newman, E., Shah, R., Haning, W., . . . Lester, B. M. (2011). Motor and cognitive outcomes through three years of age in children exposed to prenatal methamphetamine. *Neurotoxicology and Teratology, 33,* 176–184.

Sowell, E. R., Leow, A. D., Bookheimer, S. Y., Smith, L. M., O'Connor, M. J., Kan, E., . . . Thompson, P. M. (2010). Differentiating prenatal exposure to methamphetamine and alcohol versus alcohol and not methamphetamine using tensor-based brain morphometry and discriminant analysis. *Journal of Neuroscience, 30,* 3876–3885.

Substance Abuse and Mental Health Services Administration. (2011). *Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings* (NSDUH Series H-41, HHS Publication No. SMA 11-4658). Rockville, MD: Author. Retrieved from http://www.samhsa.gov/data/NSDUH/2k10ResultsRev/NSDUHresultsRev2010.htm

Zweben, J. E., Cohen, J. B., Christian, D., Galloway, G. P., Salinardi, M., Parent, D., & Iguchi, M., & the Methamphetamine Treatment Project. (2004). Psychiatric symptoms in methamphetamine users. *American Journal on Addictions, 13,* 181–190.