

Talking to Parents About Behavioral Problems in Children Following Prenatal Illicit Substance Exposure

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Case: A 36-month-old girl with a reported history of prenatal substance exposure is brought to an outpatient pediatric clinic to establish care and receive immunizations to enroll in daycare. The father reports that he became custodial parent of the child in the past week, following the mother's arrest for possession of an illegal substance. Previously, the child lived in another state with her mother and had limited contact with him. He is unaware of her medical history. When he brings her to the clinic, she is wearing her nightgown, and her hair is not brushed. She makes little eye contact and sometimes appears to actively avert her eyes. At the mention of her mother, she becomes more agitated, crying and tearing at the exam table paper, but uses few words. Her general physical exam is otherwise benign. Her father notes that he can't get her to talk and that he is overwhelmed by her screams and tantrums. He wonders if her behavior is due to prenatal drug exposure, since her mother was "taking something" while she was pregnant.

Medical professionals are likely to encounter a situation similar to the one above during their careers given that prenatal substance exposure (PSE) continues to affect many infants born in the US. Negative outcomes from PSE are varied, with the potential to cause significant harm. PSE can lead to short-term sequelae such as low birth weight, intrauterine growth restriction, and neonatal abstinence syndrome (NAS), a form of opiate withdrawal. Long-term outcomes can include behavioral and cognitive problems and early initiation of substance use.¹ Rates of PSE are difficult to estimate accurately because of stigma associated with reporting and inconsistent screening practices. Despite these difficulties, estimates exist for the proportion of children in the US who have been exposed prenatally to an illicit substance such as marijuana, opioids, cocaine, and methamphetamine (see Table 1). For example, among a nationwide sample of approximately 70,000 randomly selected individuals in the US, 4.7% of pregnant women interviewed reported use of an illicit substance within the last month.^{2,3} For perspective, consider the rising incidence of neonatal abstinence syndrome, an outcome associated with prenatal opiate exposure. According to a study conducted using two nationwide inpatient databases, the incidence of infants born in the US showing signs of NAS has been rising

since 2000, from 1.2 per 1,000 live births in 2000, to 3.4 per 1,000 in 2009, and 5.8 per 1,000 in 2012.^{4,5}

While perinatal outcomes following prenatal drug exposure have been fairly well documented, research of long-term outcomes is more limited and includes neuro-behavioral outcomes posing significant implications for clinicians, including child and adolescent psychiatrists, caring for children with a history of PSE. This article will discuss examples of large cohort studies and the methodological challenges, then describe psychoeducation statements clinicians can use based on current knowledge of long-term neurodevelopmental outcomes for children exposed prenatally to illicit substances. We will then share clinical and policy implications, as there are substantial opportunities in our field to advo-

Table 1. 2015 Drug Use Among Women Aged 15-44 by Pregnancy Status in Percentage

	PREGNANT WOMEN %	NONPREGNANT WOMEN %
Illicit drugs	4.7	12.5
Illicit drugs other than marijuana	1.8	4.3
Tobacco products	13.9	23.6
Alcohol	9.3	54.8

Note: Table data were adapted from ³.

catfor further research and services for these vulnerable children and families.

Methodologic Issues in PSE Research

There are multiple challenges in studying long-term outcomes related to PSE. Self-report of substance use by mothers may be an inaccurate report of fetal exposure due to a number of factors, including issues with underreporting due to lack of knowledge of exact substances used, difficulties recalling dose, recall bias, reliability of estimates of conception dates, and disclosure of a highly stigmatized, reportable, and potentially illegal activity. The timing of exposure affects outcomes variably depending on stages of fetal development during the PSE. Polysubstance use reporting complicates interpretation of outcomes since it is difficult to link specific exposures to specific outcomes. Studies of polysubstance use generally control for concurrent use statistically rather than in vivo. Prospective longitudinal cohort study designs necessary for long-term follow-up are limited by attrition (i.e., loss of some of the sample over time), and outcome may be affected by prenatal and postnatal environmental risk factors, which may moderate or mediate effects on the study outcomes.

Despite these challenges, a number of rigorous cohort studies reveal valuable findings about this population. For example, reviews indicate 14 different cohorts are included in studies of the effects of prenatal cocaine exposure on the developing child, including the Maternal Lifestyle Study, which has followed 1,000 children from birth into adolescence and young adulthood.⁶ The Infant Development, Environment and Lifestyle Study (IDEAL) is the only study currently in the US describing the effects of prenatal methamphetamine exposure and includes 320 children followed up to 7 years of age to date.⁷ Studies of opioid exposure show little consensus on long-term outcomes in children. Of the data that exists, methadone exposure is the most robust; however, there is a dearth of research specifically examining the effects of prenatal exposure to opiate prescription medication on long-term outcomes on development.^{1,6} The existing cohorts provide valuable information to describe the

behavioral effects of prenatal drug exposure on the developing child, albeit with limitations.

PSE Outcomes for Children and Talking Points for Families

The following section reviews the literature on PSE and outcomes in offspring, focusing on 1) perinatal outcomes, 2) longer-term psychiatric outcomes, and 3) caregiving environment. Each section is followed by a summary of clinical talking points that can be used to help families like the one presented above.

1. Perinatal Outcomes

Neonatal outcomes of PSE vary to some degree by substance but can include low birth weight, intrauterine growth restriction, NAS after opioid exposure, and other neurobehavioral effects (see Table 2).¹ The signs of NAS are summarized in Table 3. Taken together, infants with PSE may be more difficult to soothe, and parents may find it harder to interpret the infant’s cues. Importantly, perinatal outcomes may be affected by other prenatal risk factors associated with PSE, including concomitant use of licit substances such as tobacco and alcohol, poor nutrition, physical or mental health problems, and environmental stressors including violence exposure.^{8,9}

Clinical talking point: As a group, babies exposed to substances during pregnancy are at higher risk of some problems immediately after birth. However, not all babies show these problems. The specific risks for each child depend on a combination of factors that include the substance exposure, but also other prenatal experiences and factors.

Table 2: Signs of Neonatal Abstinence Syndrome	
■	Increased muscle tone and activity
■	Seizures
■	Sweating
■	Nasal flaring
■	Irritability
■	Feeding problems
■	Diarrhea

Note: See Behnke et al.¹ for further information.

Table 3. Perinatal Findings in Substance-Exposed Infants

	OPIATES	COCAINE	METHAMPHETAMINE	CANNABIS
Birthweight	↓	↓↓	↓	
Congenital anomalies	–	– (with the exception of risk of prenatal CVA)	–	–
Withdrawal	+++	–	n/a	–
Perinatal neurobehavioral changes	Diaphoresis, irritability, increased muscle tone, feeding problems, diarrhea	Irritability, state dysregulation, autonomic and behavioral dysregulation, limited alertness and orientation	Poor movement quality, decreased arousal, and increased stress ^a	Hyperstartle and tremor

Note: Table contents were adapted from Behnke et al.¹ CVA = cardiovascular abnormalities.

^a For further information, see Smith LM, Lagasse LL, Derauf C, et al. Prenatal methamphetamine use and neonatal neurobehavioral outcome. *Neurotoxicol Teratol.* 2008;30:20–28.

2. Longer-Term Psychiatric Outcomes

The long-term psychiatric outcomes for these children are complex, with both biological and environmental processes likely contributing to risk and resilience.

In their review of follow-up studies of children with prenatal drug exposure, Lester and Lagasse identified 42 studies published between 1996 and 2008 specifically looking at prenatal exposure to cocaine (PCE), methamphetamine, and opiates.⁶ In studies that controlled for confounding factors, PCE was associated with adverse outcomes in language, attention, externalizing behavior, and cognition. The Maternal Lifestyle Study (MLS)¹⁰ demonstrated the dose-dependent effects of PCE on emotional and behavioral problems. Heavy prenatal cocaine exposure was associated with an increase in the prevalence of internalizing, externalizing, and total problems in children between 3 and 7 years of age (21% vs. 16%). Importantly, despite the high media attention to cocaine exposure,¹¹ the combined effects of prenatal and postnatal alcohol and tobacco were stronger than that of heavy cocaine abuse for all ages. It should be noted that the increased rates of adverse behavioral effects with PCE compared with non-exposed children were not evident until age 5, and that life events are strongly associated with behavioral presentation.¹²

Since that review in 2010, prenatal cocaine exposure in the MLS has also been shown to be related to a need for

special education services at 7 and 11 years old, especially in children with psychopathology, a finding replicated in other but not all studies.¹³ There is a suggestion that behavioral dysregulation patterns are moderated by gender; however, findings are mixed.¹⁴ New research focuses on the role of the parasympathetic system and the hypothalamic-pituitary-adrenal axis as a mediator of dysregulation patterns.¹⁵

In the major study of prenatal methamphetamine exposure (PME), the IDEAL study, PME had no association with behavior problems at age 3, but was indirectly associated with emotional and behavioral problems at age 5, which was associated with executive functioning problems at age 6½.⁷ The association between PME and emotional and behavior problems at ages 5 and 7.5 was fully mediated by early adversity, measured at 5 time points before age 3, meaning that early adversity explains the variance in behavior problems, not the biological central nervous system effects of the methamphetamine exposure (see Figure 1). Methamphetamine exposure is, however, associated with the risk of experiencing early adversity. This study highlights the potential for interventions that target the risk of early adversity in children with PME to reduce emotional and behavioral sequelae associated with PME.

Studies focused on opiate exposure alone are more limited by sample size and less rigorous control for

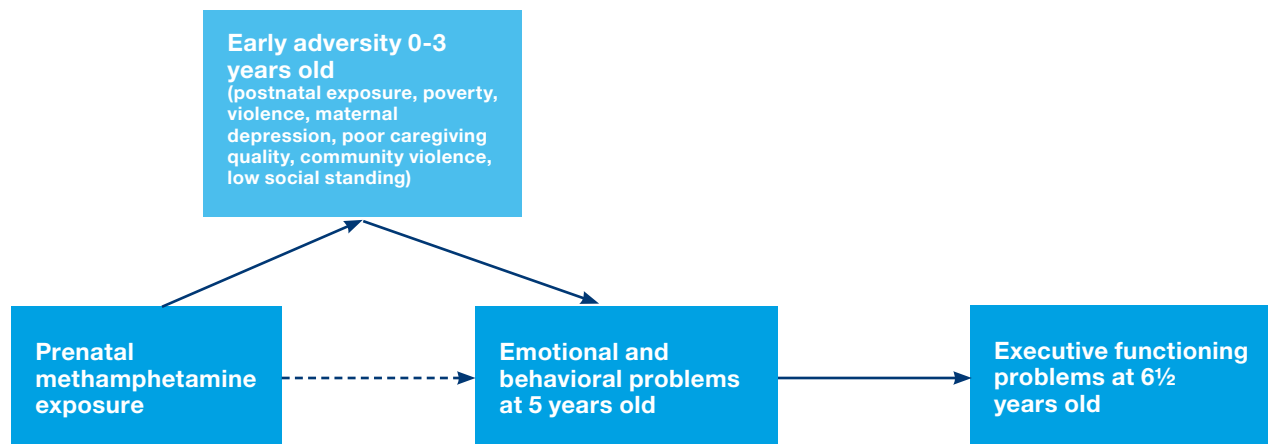


Figure 1. Early adversity mediates association between prenatal methamphetamine exposure and behavioral/emotional problems.
Note: see Abar et al.⁷ for further information.

confounding factors, but suggest the possibility of cognitive and emotional associations with the exposure.¹⁶

In the MLS, examining all PSE together, PSE predicted increases in behavioral dysregulation across adolescence directly, and indirectly was associated with increases in executive function difficulties.¹⁷ This indirect relationship was mediated by early adversity and behavioral dysregulation. Controlling extensively for potentially confounding variables, adolescents with PCE show persistent behavioral dysregulation and associated early substance use by age 16 compared to non-PCE youth (27.9% vs 19.9% in the MLS) and especially with higher rates of marijuana use (39.6% vs 16.3% in a smaller study).^{18,19} A similar pattern of early substance use has been reported in youth prenatally exposed to marijuana.²⁰

Taken together, these studies suggest that children with PSE have higher rates of behavioral problems, executive function difficulties, and early substance use and that early adversity is an important mediator in some of these associations.

Clinical talking point: As a group, older preschoolers, school-age children, and adolescents who were exposed to illicit substances during pregnancy may

have higher than usual rates of difficulty with paying attention and disruptive behaviors compared to other children their age.

3. Caregiving Environment

The current studies demonstrate that the caregiving environment plays a significant role in the behavioral outcomes of children exposed prenatally to drugs of abuse. As above, despite higher rates of some adverse behavioral outcomes, behavioral problems, executive function difficulties, and early substance use occur in a minority of children with PSE. Studies of behavioral and cognitive outcomes suggest early adversity, whose converse is a positive caregiving environment, appears to be a primary mediator of the association between PSE and behavioral dysregulation,¹⁷ suggesting quality caregiving can help ameliorate the risk for behavioral problems. One component of early adversity is a measure of the caregiving environment itself (the home) along with other components that shape a child's safety and a parent's ability to offer sensitive caregiving.

Clinical talking point: Despite the risk of difficulties children exposed to substances in utero may have, a supportive caregiving environment can be powerful and help a child develop the strengths and skills to overcome

these potential challenges. Prenatal exposure to drugs does not have to define the child's life.

Clinical and Policy Implications

The extant literature suggests that children exposed prenatally to drugs of abuse exhibit more problem behaviors and attention problems than their non-exposed peers, although a minority of children develop these clinical-level problems. The studies also demonstrate the importance of the caregiving environment in shaping behavioral regulation. The caregiving environment, especially protection from early adversity including ongoing substance use, violence, maltreatment, and symptoms of parental psychopathology, has a significant effect on the behavioral outcomes of children exposed to drugs of abuse prenatally. The finding that the caregiving environment offers protection is important since factors that contribute to the caregiving environment are responsive to change, and offer points of engagement for intervention in the lives of children.²¹

Existing literature demonstrates the substantial influence of other factors, including influences at the individual, family, community, and society level, in the clinical outcomes of children exposed to illicit substances prenatally, as represented in Figure 2.²² Individual-level

factors are controlled for in the studies reviewed above; however, these factors can have a substantial influence on a child's life. Public policy interventions can be developed to engage factors at all levels (individual, family, community, and society) and to promote resilience in children exposed to drugs of abuse prenatally.

For example, intervening at the family level, physicians and other health care providers are in a position to support parental treatment for substance abuse disorders and treatment for concurrent psychopathology. According to the National Survey on Drug Use and Health, even though women who discover they are pregnant tend to reduce their previous use of drugs, alcohol, and tobacco, most resume use following delivery.²³ Therefore, pregnancy and following delivery is an ideal time to support parents in maintaining or working towards sobriety with clinical treatment and engagement of natural supports. Screening for substance use is an important topic of conversation at all postpartum healthcare-related visits.

Child psychiatrists can play an important role in educating parents about the effects of prenatal substance exposure when seeing children who may have been exposed to PSE. This education includes acknowledging the known physical, developmental, and mental health effects of PSE as well as debunking myths that suggest that PSE fully determines a child's

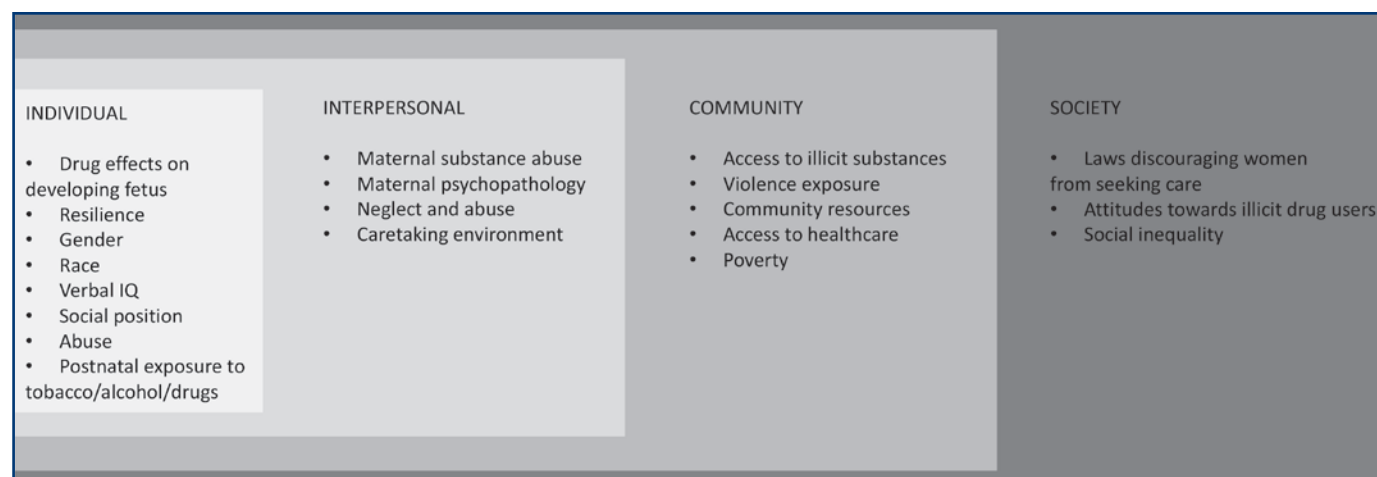


Figure 2. Social-ecological model of factors influencing psychiatric outcomes following prenatal substance exposure.

Note: see McLeroy et al.²² for further information.

life course. Children benefit when their caregivers see them as a unique individual with a balance of strengths and challenges and when caregivers are flexible in responding to a child's unique developmental path.²⁴ Clinicians can empower families with the knowledge that the caregiving environment, a modifiable factor, strongly influences a child's development. At the community and society level, physicians can advocate for policies and services that may reduce PSE by supporting women of childbearing age to engage in treatment of substance misuse, increasing access to family planning resources, and improving access to treatment of psychiatric disorders and social support services to reduce isolation. Fighting against the stigma of substance abuse disorders is necessary for women to receive treatment and for babies to benefit. Clinicians, researchers, and families can move the field forward by calling for research that investigates the mechanisms and timing by which drugs of abuse alter brain development and study interventions for children affected by PSE.

To apply this discussion to the vignette at the outpatient pediatric clinic: the clinician can explain that the child may be at higher than typical risk of behavioral dysregulation; however, studies suggest that the independent emotional and behavioral effects of PSE may no longer be evident at 36 months. Her postnatal factors—including exposure to a caregiver with an active substance abuse disorder, possible developmental delays, recent caregiving disruption (from the likely primary attachment figure, the mother, and introduction to a relative stranger, father)—may be powerful contributors to her behavior, such as her dysregulated mood with her father, as observed in the outpatient pediatrics office. Long-term psychiatric effects of prenatal drug exposure can include problems in attention, behavior, language, and executive functioning. However, early intervention that includes medical and social services can be of great benefit and target parents' drug use, improve parental functioning, and better the caregiving environment.^{25,26}

Take Home Summary

Use of illicit drugs during pregnancy carries significant stigma; however, many infants exposed to drugs of abuse prenatally have the potential to develop typically, and effects of the exposure may be ameliorated by environmental enrichment and quality caregiving.

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