

## Prenatal Alcohol and Drug Exposures in Adoption

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Families choosing to adopt domestically or internationally are faced with the possibility of prenatal substance exposure for their child. Alcohol use, drug use, and exposure to environmental agents by pregnant women can be harmful to the developing fetus, with many known short- and long-term effects on organ development, somatic growth, and neurodevelopment. As more families turn to medical providers for consultation before adoption, the challenge of accurately identifying risk factors for poor medical or cognitive outcomes becomes paramount. Prenatal substance exposure is just one of the important factors in this risk assessment, but it is one that parents frequently have questions about before and after the adoption of their child.

One of the greatest challenges when providing a preadoption medical review is obtaining accurate and complete information on children referred for adoption from different countries. Health care providers in most countries acknowledge the significance of medication and substance use in a pregnant woman. In all countries, including the United States, however, mothers may not have received prenatal care and abstracts from medical records provided for preadoptive review typically lack complete medical histories, exact amounts of the substances used, or the timing of use in a woman's pregnancy. Substance use may also be mis-translated or confused by colloquial terms from specific regions of the United States or other countries. Thus, although accurate data from the pregnancy history are crucial to helping medical professionals assess the risk of adverse neuro-

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developmental outcomes in waiting children, these data are frequently not available at the time of a preadoptive medical review.

Even with prenatal history available, it is extremely difficult to disentangle the consequences of prenatal substance exposure from the frequent comorbidities of prematurity, malnutrition, neglect, abuse, multiple placements, or institutional deprivation as discussed elsewhere in this issue. In addition, prenatal exposure to potentially harmful substances often occurs in the context of social dysfunction: poverty, parental addiction, impaired parenting, and poor access to services. A family history of mental illness or learning disabilities is often present, which can carry additional genetic risk for adoptees. In considering long-term data on outcomes in adopted children, any conclusions must control for these various mitigating factors. Nonetheless, the accurate identification of prenatal substance exposure and use of objective diagnostic techniques for fetal alcohol syndrome can help to clarify the risk of developmental outcomes for adopted children.

This article addresses the major potential prenatal substance exposures for children joining families by adoption or, indeed, by birth: alcohol, opiates, tobacco, marijuana, cocaine, and methamphetamines. For each substance, we review the teratogenicity of the exposure and identify the spectrum of neurodevelopmental issues that can present in children exposed to this substance. Diagnosis of the spectrum of fetal alcohol outcomes is also discussed. When possible, we provide country-specific statistics on exposure risks for adopted children.

## **General principles of teratology**

A teratogenic substance, whether it is a drug like alcohol or thalidomide or an exposure like radiation, is a substance that may have the potential to produce a congenital malformation. The timing of exposure in embryogenesis and dose of the exposure have an impact on whether a prenatal substance exposure leads to a malformation or other neurobehavioral manifestation later in life. Some teratogenic exposures have little risk of causing malformation if the timing and dose are below the teratogenic threshold. For example, radiation exposure is not a risk for cancer if the dose and timing of exposure are minimal. It is also difficult, in many instances, to claim a direct causal link between an exposure and an outcome. The discussion that follows incorporates data gathered from animal and human studies to describe the range of outcomes that may be related to prenatal exposures in adopted children.

## **Prenatal alcohol exposure**

### *Overview*

Fetal alcohol syndrome (FAS) is a permanent birth defect caused by maternal consumption of alcohol during pregnancy. It is a clinically defined syndrome,

characterized by growth deficiency, central nervous system (CNS) damage and dysfunction, and a unique cluster of minor facial anomalies [1,2]. Although FAS is the most extreme and recognizable expression of the adverse effects of alcohol on the developing human being, alcohol exposure can cause a range of anomalies and disabilities that fall under the umbrella of fetal alcohol spectrum disorders (FASDs) [3].

FAS has been described in all races and countries. Since its description in the medical literature in the United States in 1973 by Jones and colleagues [4], FAS has remained the leading known cause of preventable mental retardation and developmental disability in the United States [5]. The worldwide incidence of FAS is estimated at 1 to 3 per 1000 live births in epidemiologic studies [6,7]. The incidence in a foster care population in the state of Washington, a higher risk group that may be representative of many children placed for adoption, is 10 per 1000 children [8]. It is estimated that greater than 1% of all children born in the United States may have FASDs [5]. In the United States, a recent Centers for Disease Control and Prevention (CDC) survey revealed that approximately 10% of pregnant women used alcohol and approximately 2% engaged in binge drinking or frequent use of alcohol. Furthermore, more than 50% of women of childbearing age who did not use birth control reported alcohol use, and 12.4% reported binge drinking [9].

Prevalence estimates of FASDs in other countries are unclear, in part, because of disagreements regarding diagnostic criteria for the syndrome. Statistics on risk behaviors for FASDs in other countries are available, however, with country profiles of drinking patterns and trends described in the World Health Organization's "Global Status Report on Alcohol 2004" [10]. It is estimated that at least 30% of women of childbearing age in Russia drink alcohol on a regular basis [7]. Weekly alcohol use among Russian teenagers is up to 54% [11]. In Kazakhstan, the prevalence of drinking among women is lower than in Russia; however, the number of juvenile alcoholics is rapidly increasing, despite the state's effort to curb drinking [10]. China has seen a striking increase in alcohol consumption over the past decades, but social and cultural factors seem to have limited drinking among women. Unfortunately, the trends in youth drinkers and urban centers are becoming more similar to those in Western countries [12,13]. Alcohol consumption among young women in South Korea is also on the rise. It is estimated that the number of female drinkers there has increased by 3% a year since 1995, mostly because of the increased presence of women in the work force. The percentage of Korean college students who have one to three drinks per week is 96.4%, with little difference between the sexes; drinking is viewed as a good way to build social ties [14]. The lifetime prevalence of alcohol use among students in Guatemala City was found to be 26.5% [10].

### *Mechanism*

Alcohol is a known teratogen with a range of impacts on multiple organ systems, including the CNS. During gestation, alcohol exposure damages the

architecture, neuronal migration, and synaptogenesis of the developing CNS. The timing and dose of alcohol use during pregnancy are important when considering potential implications for the developing fetus. Children born to women who drink heavily on a regular basis in the first trimester of pregnancy have the greatest risk of CNS damage. The first month of pregnancy is particularly crucial for development of the CNS and the midportion of the face. Unfortunately, this early in pregnancy, many women do not realize that they are pregnant and continue their usual pattern of alcohol ingestion.

Although there is no convincing evidence to date of a “safe” threshold of prenatal alcohol consumption, one major dysmorphology textbook argues that low birth weight (LBW) and “mild” disability can be seen at an exposure of roughly 2 alcoholic drinks per day (lower in recent studies). When 4 to 6 drinks are consumed, additional clinical features become evident. Most of the children who are believed to have the full expression of FAS are born to women consuming 8 to 10 drinks or more per drinking occasion, on a regular if not daily basis, for at least the first trimester. It is estimated that the risk of a “serious problem” in the offspring of chronically alcoholic women ranges from 30% to 50%. The greatest risk is that of mental deficiency as well as a host of learning and behavioral disabilities [15].

Fetal host factors are also important in the development of FASDs. Some fetuses seem to be more susceptible to the adverse effects of alcohol use by the birth mother. For example, fraternal twins have been shown to have markedly different outcomes, even though the amount and timing of their prenatal alcohol exposure are the same. One explanation implicates genetically determined differences in the metabolism of alcohol at the fetal level because of differences in alcohol dehydrogenase activity [16].

### *Diagnosis*

There is not a uniformly agreed on approach to diagnosing FASDs. The two most widely used criteria for the evaluation of children with potential FASD continuum diagnoses are the 1996 Institute of Medicine Criteria [17,18] and the University of Washington criteria, published in 1997 and revised in 2004 [19]. The CDC has also just released new guidelines for diagnosis [20]. All proposed diagnostic methods have in common the desire to define FASD cases more clearly with objective, quantitative, and reproducible methods.

FAS is currently defined as a constellation of the following:

- Growth deficiency
- Cluster of facial anomalies, including a thin upper lip, a smooth philtrum (vertical groove between the nose and upper lip), and small palpebral fissure lengths (PFLs; width of eye openings)
- Evidence of CNS damage or dysfunction
- History of maternal alcohol use during pregnancy

To diagnose the spectrum disability of FAS, all four of these criteria should be examined.

### *Growth deficiency*

In the evaluation of growth deficiency in adopted children, there are two important considerations. Growth deficiency is the least sensitive diagnostic criterion for FAS. In many cases of clear-cut FAS, growth deficiency is not present at the time of diagnosis. In one of the longest running FAS diagnostic clinics in the country, only 40% of children who meet the facial, CNS, and prenatal exposure criteria for FAS are growth deficient (Susan Astley, PhD, University of Washington, unpublished data, 2005). These children are often referred to as having atypical FAS. Growth deficiency is not a *sine qua non* for a diagnosis of FAS.

Also, in the population of children waiting for adoption, many children without FAS are growth deficient on the basis of malnutrition and early childhood deprivation. When looking at growth deficiency as a teratogenic effect of prenatal alcohol exposure, it is important to take into consideration other explanatory factors. As a result, it may be prudent to allow time for postadoption “catch-up growth” before ranking the level of growth deficiency in a newly adopted child.

### *Facial features*

Although growth deficiency is the least sensitive criterion for FAS diagnosis, the three sentinel facial features are the most sensitive and specific. In examining a child for the facial features of FAS, there are several tools to aid in the objective evaluation of the lip, philtrum, and PFLs of children. The subject’s upper lip thickness and depth of the philtrum can be assessed and scored with the “Lip-Philtrum Guide” (Fig. 1) as originally described by Astley and Clarren [2]. Philtrum depth is ranked by holding the Lip-Philtrum Guide next to the patient’s relaxed face and selecting the picture that best matches the patient’s philtrum. Upper lip thickness is measured in the same fashion. A score of 4 or 5 is considered consistent with the thin lip and smooth philtrum characteristic of FAS. If the child is present for evaluation, PFLs can be measured in millimeters with a rigid clear plastic ruler, with the examiner seated in front of the subject. This method of eye measurement is prone to significant error in inexperienced hands, however, based on our clinic’s experience, where we compare visual estimates with computer-assisted measurements. A more accurate and reproducible method is to use FAS Facial Photographic Analysis Software to aid in assessment of facial features [21]. This image analysis software has been used as a screening and diagnostic tool for a foster care population, where it identified the facial features of FAS with 99% sensitivity and 99% specificity [8].

For use in preadoption evaluations, this software tool is most useful if the photograph being evaluated has an internal measure of scale, which allows the PFLs to be assessed accurately. In general, photographs of children forwarded for



Fig. 1. Fetal alcohol syndrome lip—philtrum guide. (Courtesy of S. Astley, PhD, Seattle, WA.)

preadoptive review are not able to be accurately assessed with this software tool unless families have taken the photographs themselves. Before traveling to a child's birth country, parents may be prepared in advance to photograph a child accurately, with an internal measure of scale allowing for later analysis. Our clinic uses an office supply sticker of known width that is placed on the patient's forehead. A close-up photograph should be taken with the patient's unsmiling and relaxed face filling the entire frame. A digital 3-megapixel (or higher resolution) camera is ideal. The lens of the camera should be directly in front of the face (the "Frankfort horizontal plane") to minimize rotation of the face

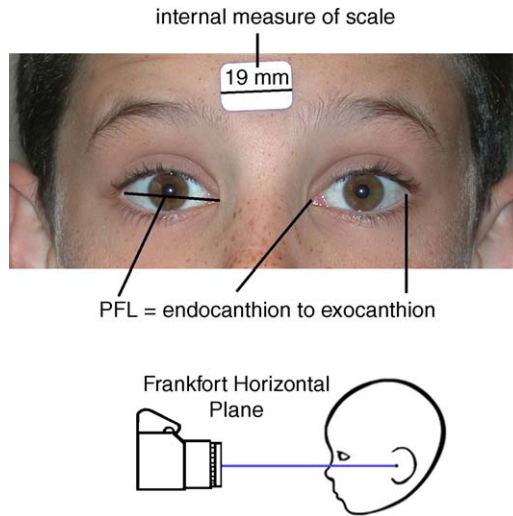


Fig. 2. Measuring palpebral fissure lengths (PFLs) using an internal measure of scale and the Frankfort horizontal plane. (Courtesy of S. Astley, PhD, Seattle, WA.)

(Fig. 2). This standardized digital frontal facial photograph is used to measure the PFLs, lip, and philtrum accurately [8]. A complete guide for how to obtain and analyze facial photographs with the use of Lip-Philtrum Guides and the FAS Facial Photographic Analysis Software can be found on the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network web site (<http://www.fasdpn.org>).

The key phenotypic FAS facial features are short PFLs, a smooth philtrum, and a thin upper lip, and the face of FAS requires all three to be present. Other features, such as epicanthal folds, a flat nasal bridge, a short upturned nose, “clown eyebrows” (often associated with microcephaly), or prominent ears, may be seen more often in children with FAS; however, they are not diagnostic because they can be normal developmental or ethnic features, especially in the international adoptee population. There is also evidence that the greater the magnitude of expression of FAS features, the higher is the risk for underlying brain damage [22].

It is far more difficult to assess a child’s potential risk of FASDs when the facial features are not extreme. For example, it is possible for an individual who is prenatally exposed to alcohol to have a completely normal facial phenotype. These individuals should still be considered at risk for learning and behavioral problems, which may be as severe as the problems faced by individuals with a FAS facial phenotype. When the FAS facial features are fully present, it is reasonable to conclude that prenatal alcohol exposure had an adverse impact on fetal development. With more normal facial features, however, it is difficult to differentiate the impact of alcohol from that of other genetic and environmental factors.

*Central nervous system damage*

CNS damage can be determined on the basis of structural malformation (eg, microcephaly or an abnormal brain MRI scan), neurologic disease (eg, seizures), or neuropsychometric data that indicate dysfunction, especially in multiple areas of cognition. Again, it is important to recognize that in the population of adopted children, poor head growth and developmental delay may also be attributable to a range of other causes, including but not limited to prenatal infections, malnutrition, early deprivation, or neurogenetic factors affecting brain growth. A period of catch-up growth and development should be allowed after a child joins his or her family before attributing CNS impairment to prenatal substance exposure. If the underlying cause of the impairment is prenatal alcohol exposure, the impairment persists.

*History of maternal alcohol use*

Maternal alcohol consumption can be difficult to quantify from adoption records. In all countries, including the United States, the exact amount, type, and timing of alcohol use during pregnancy may be impossible to ascertain.

Typical records include the following statements:

“Parents are registered as alcoholics” (Russia)

“Mother drinks but not to excess” (Kazakhstan)

“Mother drank two bottles of soju (355 mL of 25% liquor) every week until the fourth month of pregnancy” (Korea)

Alcohol use by the birth mother may be simply listed as unknown. When considering potential prenatal alcohol exposure, it is helpful to consider known risk factors frequently comorbid with maternal alcohol use. In studies conducted in the United States, women who give birth to alcohol-affected children have common psychosocial attributes. In general these women:

- Have a history of alcoholism
- Are multiparous
- Are older at the time of an affected pregnancy
- Have a history of mental illness [23]

The presence or absence of these psychosocial factors can be used for alcohol use risk stratification of birth mothers, even in the absence of a specific history in the available records. For example, if a boy born to a 40-year-old multigravida woman with a history of incarceration has a lip and philtrum of grade 4 in photographic evaluation and a borderline head circumference for his age, he should be considered at risk for alcohol-related disability even if no information about alcohol use during pregnancy is available. Because these psychosocial data describing birth mothers of alcohol-affected children were obtained in US studies, extrapolation to women in other countries should be approached with caution. In the absence of similar information from a child’s country of origin,



however, these data may help to delineate the best estimate of a child's risk for FASDs. Finally, although these comorbid factors should be taken into consideration to assess the risk or probability of prenatal exposure, they cannot be used to serve as evidence when considering an FASD diagnosis.

### *Outcomes*

As a teratogen, alcohol has been implicated in a long list of congenital defects, although our understanding of the actual rates of specific types of malformation has been hampered by lack of diagnostic consensus. Alcohol-exposed children do seem to have higher rates of eye (eg, refractive errors, strabismus, optic nerve hypoplasia), ear (recurrent otitis, conductive and sensorineural hearing loss), cleft palate, cardiac, renal, and orthopedic malformations [24].

The neurodevelopmental outcomes related to prenatal alcohol problems are varied and complex. Each child exposed to alcohol has a different neuro-behavioral profile, because the dose and timing of alcohol use in each pregnancy is unique. Each child's genetic makeup and prenatal, postnatal, and postadoptive environments also play a role in his or her outcome. Despite the lack of a specific behavioral phenotype for FAS, the literature does suggest some general patterns of disability. Manifestations of CNS dysfunction may include mental retardation or borderline IQ scores [25], neuromotor deficits, attentional issues and hyperactivity [26], and impaired social and adaptive abilities [27]. Children and adults with prenatal alcohol exposure can have unusual language and communication disabilities, particularly in the arena of social communication [28]. Subtle peripheral nerve damage leading to coordination and sensory integration problems has been described [29]. Prenatal alcohol exposure may also impair "executive functioning," the higher level cognitive functions involved in planning and guiding behavior to achieve a goal in an efficient manner [30]. Importantly, none of these neurodevelopmental patterns are pathognomonic for prenatal alcohol exposure.

These primary neurodevelopmental disabilities can cause significant impairment in an individual's ability to navigate daily activities, school, social relationships, and basic living requirements. These manifestations of FAS can lead to secondary disabilities as affected individuals with an all-too-often "invisible" disability attempt to function in society [25]. Individuals with FASDs are more likely to have a history of educational difficulties, trouble with the law, mental health problems, and substance abuse. Nevertheless, protective factors do exist, and a younger age at diagnosis and higher percentage of life in a stable and nurturing home have been shown to reduce the likelihood of these secondary disabilities [31]. Early diagnosis can help to prevent secondary disabilities by providing early intervention as well as educational and environmental support strategies [26]. Intervention projects to identify protective factors and effective interventions for individuals with prenatal alcohol exposure are currently under way. Excellent handbooks for teachers and parents of children with FASDs are available [32,33].

Children born to alcoholic parents are themselves at risk for alcoholism later in life, regardless of whether or not they have FASDs. Because the disease of alcoholism seems to have a genetic predisposition, children of alcoholic parents should start substance abuse education early, with developmentally appropriate counseling. Adoptive parents should be informed of the risk of alcoholism in their adoptive children so as to facilitate appropriate educational opportunities and to help provide an alcohol-free environment.

## **Prenatal opiate exposure**

### *Overview*

In the United States, 2.3% of pregnancies in the Maternal Lifestyle Study involved heroin or methadone exposure [34]. In international adoption, the most commonly reported prenatal opiate exposure is heroin. Heroin use has made a resurgence in recent years, particularly in Eastern Europe and the former Soviet Union. The United Nations Office for Drug Control and Crime Prevention reported that the number of known heroin addicts rose by 30% in Russia in 1999 and had quadrupled since 1995, with a current prevalence of heroin abuse at 2.1% [11,35]. In Kazakhstan, the prevalence of heroin abuse is estimated at 1.3% [35]. Opiate use is also prevalent in the countries of Southeast Asia and parts of China, particularly near areas where opium is grown and in more urban areas. Although there are no official reports from China, unofficial estimates say that there could be up to 12 million total heroin users [36]. Pregnant women who enter drug treatment programs for addiction receive another opiate, methadone, as a substitute for heroin or opium. Because drug treatment programs are on the rise in Russia and China, prenatal exposure to methadone may also occur [36,37].

### *Mechanism*

Despite the detrimental effects of opiates on the user, including the risk of addiction and exposure to the hazards of intravenous drug use (hepatitis B and C and HIV), opiate exposure to the developing fetus is not considered teratogenic. There is no known congenital malformation associated with prenatal opiate exposure. There have been harmful fetal effects described with heroin and methadone use, however, and infants born to addicted women can suffer withdrawal in the newborn period. Any child referred for international adoption with a maternal history of intravenous drug use should be considered at increased risk for HIV and hepatitis B and C.

### *Pregnancy*

LBW and symmetric intrauterine grown retardation have been reported in the offspring of heroin abusers [38]. Pregnant heroin addicts also have a statistically

significant increased risk of preterm delivery. Methadone use seems to have less effect on fetal growth and has not been shown to increase the risk of premature birth. For children born after a pregnancy complicated by opiate use, prenatal growth may be affected by maternal malnutrition and comorbid infections as well as by opiate exposure.

### *Neonatal abstinence syndrome*

Neonatal abstinence syndrome (NAS) has been well described in infants born to opiate-dependent mothers. The symptoms of NAS include CNS symptoms (eg, hyperirritability, tremors, convulsions), gastrointestinal distress, respiratory distress, and autonomic disturbances [39]. It has been reported that the infants of methadone-addicted mothers experience more severe symptoms for a longer time, partly because of the longer half-life of this opiate. Treatment of symptomatic infants generally consists of providing children with a tapering schedule of tincture of opium, morphine, or phenobarbital while monitoring clinical symptoms. During the withdrawal period, infants may dramatically influence normal caretaker interactions because they are often resistant to cuddling or soothing and have a decreased ability to respond normally to auditory or visual stimuli. The long-term impact of these early alterations in socialization may be detrimental, particularly in an orphanage setting, where nurturing caretaking may already be less frequent.

The onset of withdrawal symptoms is usually between 48 and 72 hours after birth. It is highly unlikely that a child born overseas is going to be available for adoption at this point; thus, most families adopting internationally do not directly encounter NAS. Clues to NAS may be present in the preadoption record, however, and should alert families and professionals to the possibility of prenatal opiate exposure and other risks associated with injection drug use in birth mothers (HIV and hepatitis B and C).

### *Behavior and cognition*

In some early studies, concerns about prenatal opiate exposure and poor developmental outcome were described. Reported neurodevelopmental problems included a short attention span, hyperactivity, and sleep disturbances in prenatally exposed children assessed at the age of 12 to 34 months [40]. More recent studies also suggest mild memory and perceptual difficulties in older children, but overall test scores are still within the normal range [41]. In general, it is difficult to differentiate the impact of a poor postnatal environment and prenatal heroin exposure on children's long-term outcome. One study suggests that opiate-exposed children have increased susceptibility to adverse environmental influences compared with nonexposed children [42]. Conversely, a study from Canada suggests that drug-exposed infants adopted out at birth were equivalent to Canadian matched controls in terms of educational achievement and IQ. The adopted children did, however, have increased rates of early adult depression [43].

## **Prenatal tobacco exposure**

### *Overview*

Tobacco smoking during pregnancy is one of the most ubiquitous prenatal exposures. The prevalence of smoking during pregnancy in the United States is estimated by maternal self-report at 11% and is higher in teens (18%) and women with less than 12 years of formal education (27%) [44]. Fortunately, these rates are declining [45]. In Russia, the prevalence was 16% of pregnant women in one study and seems to be increasing [46]. In Kazakhstan, it is estimated that one third of the adult population smokes [47]. In China, the prevalence of tobacco use among pregnant women has been estimated at 2% but is increasing [48], and 60% of nonsmoking pregnant women in Guangzhou had husbands who smoked [49]. The World Health Organization reports that in South Korea, 7% of women smoke tobacco; in Guatemala, 17% of women smoke [47]. True exposure rates are likely to be significantly higher, because parental self-report routinely underestimates actual exposure. Unfortunately, adoptee tobacco exposure status is often unknown.

Prenatal tobacco exposure has consistently been associated with poor fetal growth and is the single most important cause of LBW in developed countries [50]. Even environmental smoke exposure has been implicated in LBW, fetal death, and preterm delivery [51]. Myriad perinatal complications and child health problems are linked to fetal and childhood smoke exposure. Finally, a growing body of evidence is implicating smoking during pregnancy in a range of adverse behavioral and cognitive outcomes.

### *Mechanism*

Cigarette smoke contains tar, nicotine, and carbon monoxide. Tar contains numerous substances (lead, cyanide, cadmium, and more) known to be harmful to the fetus [52]. Nicotine readily crosses the placenta and distributes freely to the CNS, having direct and indirect effects on neural development [38]. Intrauterine hypoxia, mediated by carbon monoxide and reduced uterine blood flow, is a major mechanism of the growth impairment linked to prenatal tobacco exposure.

### *Pregnancy*

Tobacco smoking during pregnancy has been associated with placenta previa, placental abruption, premature rupture of membranes, preterm birth, intrauterine growth restriction, and sudden infant death syndrome (SIDS) [53]. A dose-dependent association with cleft lip anomalies has also been noted [54].

Tobacco's impact on fetal growth is perhaps the most consistent and concerning, given the range of potential impacts on health and developmental outcomes. Maternal smoking has an impact on fetal growth symmetrically in a dose-related fashion [55] and causes an estimated 5% reduction in relative

weight for every pack of cigarettes smoked per day [56]. Because pregnant women who smoke deliver babies weighing 150 to 250 g less than babies of nonsmokers, tobacco smoking essentially doubles the chance of having a LBW baby [57]. Unfortunately, maternal smoking is also associated with a smaller head circumference at birth [58].

### *Child health*

It is difficult to differentiate the impact of prenatal smoking and environmental tobacco smoke on childhood health problems, such as respiratory and ear infections, pulmonary function, asthma, and SIDS. Postnatal smoke exposure increases the incidence of middle ear disease, asthma, wheeze, cough, phlegm production, bronchitis, bronchiolitis, pneumonia, and impaired pulmonary function, and it has also been associated with snoring, adenoidal hypertrophy, tonsillitis, and sore throat [59]. Smoking during pregnancy does cause poor lung growth, affecting pulmonary function in infancy and childhood [60,61], and seems to confer additional risk to postnatal smoke exposures [62].

With respect to tobacco-associated growth impairment, children generally demonstrate “catch-up” with their weight and height percentiles during their first few years of life, with less catch-up noted in head circumference [63,64]. In fact, a trend toward obesity is noted [65].

### *Behavior and cognition*

Dose-effect impacts of prenatal tobacco exposure on behavioral and cognitive outcomes of children have been reported, even after controlling for confounders like socioeconomic status, parental education and mental health, prenatal growth, other prenatal exposures (eg, alcohol), and postnatal disadvantages [66].

Infants born to mothers who smoke tobacco display higher rates of impaired neurobehavior, with reduced habituation, lower arousal, hypertonicity and tremors, sucking difficulties, worse autonomic regulation, and altered cries [67]. Nursery evaluations suggest a withdrawal effect as well [68]. The international adoptee population seems less likely to have these dysregulations repaired by consistent and regulating caregiving while residing in a hospital or orphanage.

There is a consistent association described between prenatal exposure to tobacco and attention deficit hyperactivity disorder (ADHD)-like symptoms [67] and externalizing behavior problems [69,70]. Antisocial traits like disruptive behavior, conduct disorder, and later delinquency have been linked to prenatal tobacco exposure as well [71]. Although these associations are clear, proving the causal relation is challenging, because not all these studies control for confounders, such as prenatal alcohol exposure.

There is a stronger link between prenatal smoking and behavioral outcomes than that described with impaired cognition. Smoking during pregnancy was associated with decreased IQ scores for children by an average of 4 points [72], however, which was prevented by smoking cessation [73]. Other studies are

inconsistent but have suggested persistent deficits in auditory-related tasks like verbal memory, language, and auditory processing [74].

It is unclear if these outcomes can be attenuated by nurturing and regulating home environments and to what extent the effects of tobacco interact with other biologic, prenatal, and postnatal risk factors. For internationally adopted children, the potential interaction of these developmental modifiers seems particularly complex, with tobacco-associated risks (eg, LBW and microcephaly, infant neuro-behavior, toddler negativity [75], childhood attention and/or impulse control deficits, antisocial behavior) occurring within a trajectory of caregiving moving from early institutional neglect to later nurturing and stimulating family environments.

## **Prenatal marijuana exposure**

### *Overview*

Marijuana is a popular recreational drug in many parts of the world. In the United States, 22% of high school students have used marijuana in the past month [76]. Estimates of marijuana use during pregnancy vary between 2% in broad surveys using maternal self-report [77] and 20% to 27% in higher risk populations using urine screens [78,79]. In the experience of our international adoption clinic, referrals outside North America have not included reports of prenatal marijuana exposure, but the United Nations Office on Drugs and Crime (UNODC) estimates that the annual prevalence of marijuana use is 3.9% in the Russian Federation, 2.4% in Kazakhstan, 0.3% in China, 0.1% in South Korea, and 3.2% in India [35]. In Guatemala, where the rate of drug consumption among young people is on the rise, marijuana consumption by teenagers is at 4% to 6.7% [80].

### *Mechanism*

The principle psychoactive substance in marijuana,  $\Delta$ -9-tetrahydrocannabinol (THC), rapidly crosses the placenta and may remain in the body for 30 days before excretion, thus prolonging potential fetal exposure. THC is also secreted in breast milk. Marijuana smoking produces higher levels of carbon monoxide than tobacco [38], which is hypothesized to be a potential mechanism of action of prenatal marijuana exposure's impact on the developing fetus.

### *Pregnancy*

Marijuana use during pregnancy may have a modest effect on prenatal growth, but the results are inconsistent from study to study and diminish when potential cofounders are controlled [81–84]. These effects, if any, are not associated

with later growth deficiency, although a few studies have suggested an impact on height [81] as well as persistent negative effects on head circumference in the offspring of heavy marijuana users [63]. This review found no consistent link between prenatal marijuana exposure and other adverse pregnancy outcomes or congenital malformations [85].

### *Behavior and cognition*

Subtle effects of prenatal marijuana exposure on cognition have been observed in two large well-controlled study groups: a predominantly low-risk Ottawa cohort and a higher risk Pittsburgh population. The Ottawa authors argue that although prenatal tobacco exposure is associated with deficits in IQ, impulse control, and other fundamental aspects of performance, prenatal marijuana exposure does not impair IQ or basic visuoperception but influences the application of these skills in problem-solving situations requiring visual integration, analysis, and sustained attention [86]. Marijuana is thus argued to have an impact on higher level executive function and performance in a “top-down” fashion, in contrast to tobacco’s “bottom-up” effects [87]. The Pittsburgh study group finds links to inattention and/or impulsivity [88] and subtle deficits in memory and learning [89]. This group also connects prenatal marijuana exposure with academic underachievement, perhaps reflecting less buffering of marijuana’s effects by environment in this higher risk population [90].

## **Prenatal cocaine exposure**

### *Overview*

Cocaine has received much attention since the 1980s, when crack cocaine began to plague urban America. Early alarmist predictions about an epidemic of neurologically damaged “crack babies” gave way to guarded optimism with early reports of neurodevelopmental functioning reporting no differences attributable to cocaine exposure. Follow-up studies with more specific measures, however, suggest effects of prenatal cocaine abuse on aspects of neurobehavior and language, as demonstrated with specific developmental tasks.

The rate of prenatal cocaine exposure in the United States ranges from 0.3% to 31% depending on the population surveyed and method of ascertainment [77,78] and was 10% in the ongoing Maternal Lifestyle Study [34]. In our clinic’s experience, reports of cocaine exposure in the international adoptee population are quite rare. The UNODC estimates the lifetime prevalence of cocaine consumption to be approximately 2% to 5% in a study of Guatemalan teenagers; in Russia, China, Korea, and other frequent countries of international adoption, the prevalence seems to be much less [35].

### *Mechanism*

Cocaine and its metabolites readily cross the placenta, concentrating in amniotic fluid, and may produce direct neurotoxic effects, disturb monoaminergic (eg, dopamine, norepinephrine, serotonin) pathways, and cause vascular-mediated damage [91].

### *Pregnancy*

The use of cocaine in pregnancy has been associated with a number of obstetric complications, such as stillbirth, placental abruption, premature rupture of membranes, fetal distress, and preterm delivery [92]. Growth restriction is often reported but may require higher levels of exposure and does not seem to persist after birth [93]. There may be a dose-response effect of cocaine on newborn head circumference [94]. Other CNS lesions (eg, stroke, cystic changes, possible seizures), cardiac defects, and genitourinary (GU) anomalies have also been reported, but the few available large, controlled, population-based studies on cocaine exposure and malformations have reached contradictory conclusions [95].

### *Behavior and cognition*

Prenatal cocaine abuse may cause specific neurobehavioral and learning problems, although it is not associated with global cognitive deficits [96,97]. The largest matched cohort study to date found no significant covariate-controlled associations between cocaine exposure and mental, psychomotor, or behavioral functioning through 3 years of age [98]. Infant neurobehavioral abnormalities like irritability or excitability, sleep difficulties, and state regulation difficulty as well as transient neurologic abnormalities like tremor, hypertonia, and extensor posturing have been reported [99,100]. Heavy prenatal cocaine use has been linked to poor memory and information processing in infancy [101]. At 3 years of age, increased fussiness, difficult temperament, and behavior problems were described [102]. Language delay has also been described, with foster or adoptive caregiving described as a promising protective factor [103,104].

## **Prenatal methamphetamine exposure**

### *Overview*

Methamphetamine abuse has increased dramatically in the United States in the past decade, especially in the western and midwestern states [105]. In Russia, cheap imported heroin still prevails, but abuse of home-produced ephedrine-based “vint” and other injectable amphetamines is on the rise and already predominates in certain cities, including Vladivostok and Pskov [106]. Methamphetamine abuse is a significant problem in Southeast Asia as well, with 19% of



Thai female students using methamphetamine in one school-based study [107]. The UNODC reports large increases in methamphetamine production and abuse in China, Singapore, and Thailand [35]. Because methamphetamine is relatively cheap to manufacture from readily available products, “home labs” are becoming increasingly common in many parts of the world. Unfortunately, the chemicals and byproducts involved are highly toxic and flammable.

Methamphetamine is a CNS stimulant that releases large amounts of dopamine, resulting in a sense of euphoria, alertness, and confidence [108]. It can be injected, smoked, snorted, or ingested orally. Prolonged use at high levels results in dependence and erratic behavior [105]. Evidence on the effects of prenatal methamphetamine use is still emerging, but effects on prenatal growth, behavior, and cognition have been described.

### *Mechanism*

Studies of adult methamphetamine abusers have shown potential neurotoxic effects on subcortical brain structures, namely, decreased dopamine transporters, brain metabolism, and perfusion [108]. Although the impact of methamphetamine use during human pregnancy is currently unknown, animal studies have demonstrated neurotoxic effects of amphetamines and remodeling of synaptic morphology in response to prenatal methamphetamine exposure [109]. One study did describe a smaller putamen, globus pallidus, and hippocampus in methamphetamine-exposed children [108].

### *Pregnancy*

Women using methamphetamine during pregnancy may have an increased rate of premature delivery and placental abruption [110]. Methamphetamine use during pregnancy is linked to fetal growth restriction and, occasionally, withdrawal symptoms requiring pharmacologic intervention at birth [111]. Clefting, cardiac anomalies, and fetal growth reduction have been described in infants exposed to amphetamines during pregnancy. These findings have been reproduced in animal studies [112].

### *Child health*

Late effects on child health resulting from prenatal methamphetamine use are unknown. Children who live at or visit methamphetamine home labs face acute health and safety hazards from fires, explosions, and toxic chemical exposures, however. The caregiving environments of methamphetamine users are often characterized by chaos, neglect and abuse, and criminal behavior as well as the presence of firearms, contaminated sharps, and other risks [113].

*Behavior and cognition*

The scant research describing the outcomes of methamphetamine-exposed children describes possible links with aggressive behavior, peer problems, and hyperactivity [114,115]. A small recent study found that methamphetamine-exposed children scored lower on measures of visual motor integration, attention, verbal memory, and long-term spatial memory [108]. In rats, even low doses of prenatal methamphetamine exposure can alter learning and memory in adulthood [116].

**Preadoption consultations case***Baby A*

Baby A is waiting in an orphanage in a country overseas. She was born at an estimated 37 weeks of gestation after a reportedly uncomplicated pregnancy with no prenatal care. Apgar scores were reportedly normal. Growth parameters at birth were all reportedly in the fifth percentile at birth. The medical excerpt reports that the birth mother smoked and “used alcohol.” There are no other prenatal substance exposures noted.

Baby A was her birth mother’s eighth pregnancy and fifth delivery. The birth mother was 36 years of age at the time of delivery. Nothing else is known about the birth mother’s mental or physical health or the health or whereabouts of the baby’s birth father or siblings.

Baby A came to orphanage care from a hospital at 6 months of age after the parental rights were involuntarily terminated. On arrival at the orphanage, growth deficiency was noted but no other physical abnormalities were detected by the physicians. Her current growth includes height, weight, and occipital frontal circumference (OFC) at the third percentile. Her development is reportedly “adequate” now at 12 months of age. She is crawling, vocalizing, and manipulating objects. She smiles and laughs with familiar caregivers.

*Baby B*

Baby B is in foster care awaiting adoption. She was born prematurely at 31 weeks of gestation to a 20-year-old mother with a history of narcotic abuse during pregnancy. No alcohol use was noted in the chart. Late prenatal care was received. The birth mother has a history of depression, and the birth father has a history of learning disabilities and attentional problems. He is currently incarcerated. There are no siblings. Baby B’s Apgar scores were 5 and 7, and the postnatal course was complicated by “mild” NAS. No other major problems occurred in the newborn period. The infant was discharged to foster care after

4 weeks in the hospital and has been in the same foster home for 12 months. Her growth parameters (height, weight, and OFC) at birth were in the 20th percentile adjusted for prematurity and have remained in that range over time. She is reportedly developing normally for her adjusted age. She also crawls, vocalizes, manipulates, smiles, and laughs.

### *Case discussions*

In both cases, we have children at risk for future learning and behavior problems. This discussion focuses on the considerations during a preadoptive evaluation and when considering overall risk assessment.

Baby A's risks involve alcohol exposure in utero as well as a postnatal history of neglect and suboptimal stimulation while residing in an institutional setting. Although her growth and development are delayed for her stated age, these could be products of her environment rather than the teratogenic effect of alcohol. Without prenatal care documenting growth and development over time, the gestational age described at birth may be erroneous. It is important for the family to obtain as many details as possible about the birth mother's alcohol use, history of other mental or physical health issues, and circumstances surrounding termination of parental rights. Risk factors for heavy alcohol exposure include maternal age and parity. Photographic evaluation of this child's face for FAS is also crucial in helping to predict the risk and potential magnitude of learning and behavioral issues. Finally, the absence of documentation of parental mental or medical illness should not be equated with negative findings, because this information is often not gathered before referral for adoption.

Baby B's risks for long-term learning and behavior issues include prenatal substance exposure. It is important to recognize that when narcotic abuse is listed as the major exposure, there may be alcohol exposure as well. Many drug abusers do not consider drinking alcohol to be their "problem," even if their level of alcohol use could have a significant impact on the developing fetus. Baby B should also have evaluation of her facial features for FAS.

Baby B has had a more stable environment than baby A in these scenarios, and more is known about the family history. Baby B is more overtly at risk for learning and mental health issues, given her reported family history, although Baby A may also have genetic issues that have not been identified or disclosed.

Like Baby A, Baby B's development is also reasonable for her age when adjusted for prematurity. This early development is not a good predictor of long-term cognitive development for either child, however. Difficulties in behavioral regulation, language, memory, problem solving, and higher order thought processes (including "executive functioning") may not appear until later in life. Both children should be followed closely for learning and behavior issues related to prenatal substance exposure, prematurity, postnatal events, and family history. Given the family histories disclosed, both children have their own risk of substance abuse later in life.

## Summary

Prenatal alcohol and drug exposures are of significant concern in many domestic and international adoptions. Unfortunately, the rates of these substance exposures are on the rise in many countries of origin. Pregnancy complications, premature birth, prenatal and postnatal growth deficiency, congenital defects, withdrawal syndromes, infant neurobehavioral dysregulation, and complex childhood behavioral and cognitive deficits can all result from such prenatal exposures. This review, and most of the research literature, has examined each of these alcohol and drug exposures one by one. In reality, polysubstance exposure is perhaps more common; however, to date, we have little understanding of how these and other prenatal exposures interact with each other to affect the developing fetus.

For children of adoption, it is sobering to consider how these substance exposures, in combination with other social and biologic risks, may make affected children more vulnerable to the adverse effects of malnutrition, neglect, abuse, multiple placements, or institutionalization. At a minimum, it seems less likely that early neurobehavioral problems can be repaired in such environments. Conversely, adopted children are typically received into loving and nurturing homes with motivated and resourceful parents. This is a remarkable intervention in and of itself, affording children with multiple vulnerabilities the opportunity for catch-up growth and development, formation of stable and secure attachments, early diagnosis of primary disabilities, appropriate services, and prevention of secondary disabilities. The lifelong impact of this caregiving trajectory on the long-term effects of prenatal alcohol and drug exposures remains to be seen.

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