Chapter 3
In Utero Exposure to Nicotine, Cocaine, and Amphetamines

Lynn T. Singer, Meeyoung O. Min, Adelaide Lang, and Sonia Minnes

Introduction

Nicotine, cocaine, and amphetamines (methamphetamine, amphetamine, and 3,4, methylenedioxymethamphetamine, "MDMA or Ecstasy") are psychomotor stimulants, a class of drugs in which significant sensorimotor activation occurs with drug administration (Meyer & Quenzer, 2005). Stimulants are drugs that enhance alertness and attention, increase arousal and behavioral excitement, and have a high potential for producing mental and physiological dependence. They vary in their legality, therapeutic use, mode and pattern of intake, pharmacologic actions, and prevalence of use, as well as in the sociodemographic and personality characteristics of women who choose to continue to use them during pregnancy despite strong medical contraindications. Importantly, our understanding of the effects of these stimulants on fetal and child developmental outcomes varies considerably across specific substances. Some stimulants, such

L.T. Singer, Ph.D. (✉)
Case Western Reserve University, 2040 Adelbert Road, Cleveland, OH 44106, USA
e-mail: Lynn.Singer@case.edu

M.O. Min, Ph.D. • S. Minnes, Ph.D.
Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106, USA
e-mail: Meeyoung.Min@case.edu; Sonia.Minnes@case.edu

A. Lang, Ph.D.
Case Western Reserve University, 11635 Euclid Avenue, Cleveland, OH 44106, USA
e-mail: Adelaide.Lang@case.edu

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as cocaine and nicotine, are subjects of a large body of research, while there is virtually no information on the effects of prescribed amphetamines or MDMA on long-term child development.

A significant issue in current research on the behavioral teratology of stimulants is that women who use stimulants during pregnancy, particularly those that are illegal, are virtually all polydrug users. They also tend to be heavier users of other drugs, such as marijuana, opiates, and alcohol that serve to mitigate the excitatory "highs" of stimulants. Thus, untangling the prenatal effects of any one drug on child development becomes difficult because stimulant drugs are likely to cause dependence and are rarely used alone. In studies of cocaine-exposed infants, their mothers self-reported using higher amounts of alcohol, marijuana, and nicotine during pregnancy in addition to cocaine than did control groups in which women reported alcohol, marijuana, and nicotine, but not cocaine use (Coles, Bard, Platzman, & Lynch, 1999; Eyler, Behnke, Conlon, Woods, & Wobie, 1998; Singer, Arendt et al., 2002). Similarly, in a study in the UK, the majority of women who used MDMA recreationally during pregnancy also used alcohol, tobacco, and marijuana, as well as psychedelic drugs like LSD and ketamine (Singer et al., 2012a).

Other factors affecting understanding of the outcomes of children exposed to stimulants in utero are the legality of the drug as well as the psychological and sociodemographic characteristics of the users. Exposure levels to illegal stimulants, such as cocaine, MDMA, and methamphetamines, are difficult to quantify accurately, while nicotine and prescription stimulant amphetamines, such as Ritalin, Concerta, Adderall, and Vyvanse, are federally regulated and provide more precise measures of the dose of drug exposure to the fetus if maternal reports are accurate. With illegal stimulants, data may be unreliable as fear of incarceration or loss of child custody may lead pregnant women to deny or minimize the amount of the drug used. However, even when legal, when harmful effects to the fetus are widely publicized, such as with alcohol or tobacco, pregnant women are reluctant to admit use to avoid social disapproval, so that denial or minimization of use occurs.

Finally, assessing the relative risks of various stimulants is difficult because the type of stimulant used by women during pregnancy is frequently confounded with the social and psychological characteristics of the users. The extensive data base now available on the sequelae of prenatal cocaine exposure is derived primarily from studies of offspring of poor, urban, largely minority women recruited during the "crack-cocaine" epidemic of the late 1980s and 1990s in the USA. There are no comparable studies available for children of women of middle socioeconomic status, so it is difficult to separate the biological effects of cocaine exposure from the effects of violence exposure, poor education, and poverty of the cohorts studied. The few studies available of prescription amphetamines, alternatively, are derived from studies of middle socioeconomic status volunteers with preexisting attentional deficits, so that effects on offspring may not be generalizable to other populations that do not share genetic factors or caregiving characteristics associated with a parent with ADHD. Despite these caveats, a substantial body of research that can begin to inform public health efforts for prevention and intervention has begun to emerge documenting the outcomes of various cohorts of children exposed prenatally to

stimulants. In light of the different research findings associated with different types of stimulants, in this chapter we discuss the developmental outcomes of in utero exposure to nicotine, cocaine, and amphetamines in separate sections.

Nicotine

Definitional Issues and Prevalence

Nicotine, an alkaloid found in tobacco leaves, is the primary psychoactive component of tobacco. While there are over 4000 chemicals in tobacco smoke that may be toxic, substantial evidence exists that nicotine is a key ingredient with adverse effects on brain development (Dwyer, McQuown, & Leslie, 2009). Despite widespread public health warnings, about 15.4 % of pregnant women aged 15–44 in the USA smoke tobacco during their pregnancies (Substance Abuse and Mental Health Services Administration, 2014). While some women quit smoking prior to or during pregnancy, about 10.7 % of pregnant women continue to smoke through their third trimester. Smoking during pregnancy occurs in all socioeconomic and ethnic groups, but rates are higher in low socioeconomic populations, those under age 25, and those with less education. Of those who quit smoking during pregnancy, up to 40 % relapse within 6 months after delivery (Centers for Disease Control and Prevention, 2013). Thus, adverse effects of smoking can continue after birth by transmission through breast milk (Primo, Ruela, Brotto, Garcia, & Ede Lima, 2013) and exposure to second hand smoke (US Department of Health and Human Services, 2006).

Impact on the Developing Child

Nicotine crosses the placenta readily and may reach fetal concentrations much higher than maternal levels, contributing to reduced oxygen supply, undernourishment of the fetus, and vasoconstrictor effects on the placenta and umbilical cord (Behnke, Smith, Committee on Substance Abuse, & Committee on Fetus and Newborn, 2013). The adverse physical effects of smoking during pregnancy include increased risk for miscarriage, stillbirth, infant mortality, Sudden Infant Death Syndrome (SIDS), preterm birth, fetal growth retardation, and low birthweight (National Institute on Drug Abuse—US Department of Health and Human Services, National Institutes of Health, 2012). Relationships between maternal smoking in pregnancy and childhood obesity, elevated blood pressure, and Type II diabetes have also been found (Rogers, 2009). Exposure to secondhand smoke can cause additional health problems such as asthma attacks, bronchitis, respiratory infections, ear infections, and SIDS (Centers for Disease Control and Prevention, 2014, March 5).

Animal studies indicate that prenatal exposure to nicotine disrupts the timing of trophic events linked to nicotinic cholinergic receptors, leading to premature onset of cell differentiation at the expense of replication, alteration of cell signaling, brain cell death or structural alterations in regional brain areas, and effects on the neurotransmitter systems involving dopamine, serotonin, and norepinephrine (Slikker, Xu, Levin, & Slotkin, 2005). In rats, these brain changes are associated with locomotor hyperactivity and reduced cognitive function. A review of the literature on brain structure and function in humans (Bublitz & Stroud, 2012) indicates that prenatal nicotine exposure is associated with decreased volume/thickness of the cerebellum and corpus callosum, increased auditory brainstem responses in infants, and lack of coordination across brain regions in response inhibition, memory, and attention tasks in adolescents. Alterations in these brain regions have also been linked to deficits in cognitive abilities, auditory processing, social development, and ADHD.

Numerous studies have identified neurobehavioral abnormalities in nicotine-exposed infants including greater excitability, arousal, muscle tension, more signs of stress/abstinence, greater need for touch to be calmed, poorer self-regulation, and greater negative affect (Barros, Mitsuhiro, Chalem, Laranjeira, & Guinsburg, 2011; Law et al., 2003; Schuetze & Eiden, 2007; Stroud et al., 2009) compared to unexposed infants. This early compromised neurobehavior may predict persistent adverse outcomes in childhood, particularly behavioral difficulties (Hernandez-Martinez, Arija Val, Escribano Subias, & Canals Sans, 2012; Stroud et al., 2009).

Intellectual Functioning

Many studies have found a relationship between prenatal nicotine exposure and lower IQ scores on intelligence measures across childhood and adolescence. A systematic review of the literature (Clifford, Lang, & Chen, 2012) indicated that the reductions in IQ tend to be small and effects sometimes attenuated or eliminated after adjustment for maternal intelligence, maternal education, SES, sibling relationships, and infant birth weight. Heavier exposure to nicotine is associated with lower overall intelligence scores (Batty, Der, & Deary, 2006; Fried, Watkinson, & Gray, 2003; Mortensen, Michaelsen, Sanders, & Reinisch, 2005).

Academic Functioning

A limited number of studies investigated the link between prenatal tobacco exposure and academic achievement. In one prospective birth cohort study, school age children of mothers who smoked during pregnancy performed more poorly on tests of arithmetic and spelling, after adjustment for risk factors (Batstra, Hadders-Algra, & Neeleman, 2003). Other studies found dose–response associations between exposure and school age children's reading skills after adjusting for socioeconomic status, type of school attended, and prenatal and postnatal characteristics (Cho, Frijters, Zhang, Miller, & Gruen, 2013; Fried, Watkinson, & Siegel, 1997). In studies that measured academic achievement using school grades or grade point average

(D'Onofrio et al., 2010; Lambe, Hultman, Torrang, Maccabe, & Cnattingius, 2006; Martin, Dombrowski, Mullis, Wisenbaker, & Huttunen, 2006) exposed children (age 12) and adolescents (age 15) had a higher risk of lower grade performance compared to non-exposed peers. However, when compared to siblings differentially exposed to maternal smoking during pregnancy, there were no differences in academic achievement in two large epidemiological studies (D'Onofrio et al., 2010; Lambe et al., 2006), suggesting the confounding role of genetic and familial factors.

Neuropsychological Functioning

Studies investigating the effect of prenatal nicotine exposure on executive functions such as memory, attention, self-regulation, and response inhibition have produced mixed findings. At preschool age, nicotine-exposed 4-year-old children demonstrated poorer selective attention than unexposed children (Noland et al., 2005). Maternal smoking during pregnancy was also associated with a decrease of 4-year-old children's global cognitive scores, and poorer executive function and working memory (Julvez et al., 2007). In 3-year-old children, prenatal tobacco exposure was related to lower motivational, but not cognitive self-regulation (Wiebe et al., 2015).

At school age, prenatal cigarette exposure has been associated with impaired speed of executive attention in 5–7-year-old children (Mezzacappa, Buckner, & Earls, 2011). Seven- to nine-year-olds exposed to prenatal smoking had poor emotional inhibitory control in a dose response manner but no relationship was found on a measure of cognitive inhibitory control (Huijbregts, Warren, de Sonneville, & Swaab-Barneveld, 2008). Significant associations between prenatal tobacco exposure and 10-year-olds' lower performance on tasks measuring verbal learning, design memory, problem solving, mental flexibility, and eye-hand coordination were reported (Cornelius, Ryan, Day, Goldschmidt, & Willford, 2001) but no differences were found in attention deficits or increased activity on a continuous performance task.

In adolescence, a relationship between prenatal cigarette smoking and auditory memory has been noted (Fried et al., 2003). However, an extensive neuropsychological battery of cognitive tests given to a large sample of 12–18-year-olds with and without prenatal nicotine exposure found no effects on any cognitive ability (IQ, academic achievement, executive functions) with cases matched by maternal education (Kafouri et al., 2009). The wide variety of neuropsychological measures used across different methodological approaches makes it difficult to draw definitive conclusions about prenatal nicotine exposure and its impact on specific executive function abilities (Clifford et al., 2012).

Language Functioning

Prenatal tobacco exposure has been linked to reduced language skills in childhood. In a polydrug exposed sample of children followed prospectively from birth to age 6, cigarette exposure was associated with lower receptive language scores (Lewis, Kirchner, et al. 2007). Lower auditory processing and receptive language skills have

also been reported through age 12 (Fried et al., 1997). One large prospective birth cohort related higher prenatal nicotine exposure to poorer performance on language tasks and increased risk of language impairment at age 8 after adjusting for socioeconomic status, type of school attended, and parental interaction (Eicher et al., 2013).

Emotional and Behavioral Functioning

There are mixed findings on the association between prenatal nicotine exposure and child internalizing symptoms such as depression or anxiety, with some studies finding an association (Ashford, van Lier, Timmermans, Cuijpers, & Koot, 2008; Menezes et al., 2013; Moylan et al., 2015), while others did not (Brion et al., 2010; Lavigne et al., 2011). Prenatal nicotine exposure has been linked to a range of externalizing behavior problems consistently including inattention, hyperactivity, impulsivity, oppositional behavior, aggression, rule-breaking, delinquency, and peer problems, across childhood and adolescence (Cornelius et al., 2011; Cornelius, Goldschmidt, DeGenna, Day, & Goldschmidt, 2007; Day, Richardson, Goldschmidt, & Cornelius, 2000; Gatzke-Kopp & Beauchaine, 2007). Whether these effects are causal or due to genetic and other family environment factors remains a question (D'Onofrio et al., 2008, 2012; D'Onofrio, Van Hulle, Goodnight, Rathouz, & Lahey, 2012). A recent genetically sensitive study that examined the relationship between maternal smoking during pregnancy and conduct problems in children reared by biological and adoptive mothers across three pooled study samples found smoking during pregnancy to be a risk factor for offspring externalizing behavior problems even after control for child-rearing practices and the home environment (Gaysina et al., 2013). A comprehensive overview of prenatal nicotine exposure and behavioral findings of attentional, externalizing and internalizing problems concluded there is evidence of increased risk of conduct or externalizing problems in children (Tiesler & Heinrich, 2014).

Prenatal nicotine exposure increases the risk of early tobacco use as well as multiple substance use in adolescents (Goldschmidt, Cornelius, & Day, 2012; Lotfipour et al., 2009). Family background factors (D'Onofrio, Rickert, et al., 2012; D'Onofrio, Ricker, et al., 2012) and current maternal smoking and peer smoking (Cornelius, Leech, Goldschmidt, & Day, 2005) likely play confounding roles. Maternal smoking during pregnancy has been associated with increased risk of nicotine dependence in offspring (Buka, Shenassa, & Niaura, 2003), nearly doubling the risk that the child will meet diagnostic criteria for lifetime tobacco dependence in adulthood, if that child starts smoking.

Specific Diagnostic Outcomes

Maternal smoking during pregnancy is one of the most commonly cited prenatal risks associated with ADHD, with dose–response relationships evident (Thapar, Cooper, Eyre, & Langley, 2013). The risk of developing ADHD in children exposed

in utero to nicotine ranges from 2.4 to 3.4 times higher than among unexposed children (Zhou et al., 2014). It is unclear whether the association is causal or due to confounding genetic or other household-level factors, in light of studies finding no association with increased ADHD risk that controlled for these factors (D'Onofrio et al., 2008; Thapar et al., 2009).

Support for the association of smoking during pregnancy and the diagnosis of conduct disorder (CD), a severe and persistent pattern of antisocial behavior, has also been found (Wakschlag, Pickett, Cook, Benowitz, & Leventhal, 2002). In particular, children born to mothers who smoke more than a half pack of cigarettes per day during pregnancy are up to four times more likely to have CD, and to have increased rates of oppositional defiant disorder (ODD) (Zhou et al., 2014). While some argue that these findings cannot be interpreted as causal (D'Onofrio, Van Hulle, et al., 2012), others (Slotkin, 2013; Tiesler & Heinrich, 2014) believe that the bulk of the evidence supports prenatal tobacco exposure as contributing to subsequent conduct problems in offspring.

Prognosis and Moderating Factors

The adverse effects of prenatal nicotine exposure on cognitive and behavioral outcomes have been shown to persist well into young adulthood (Cornelius, Goldschmidt, & Day, 2012; Mortensen et al., 2005). Low birth weight, maternal intelligence and education, SES, and other family environment factors (e.g., learning stimulation in the home) all play a role in the relationship between exposure and cognitive functioning (Clifford et al., 2012). A number of moderating factors have been demonstrated in the pathway from prenatal tobacco exposure to disruptive behaviors as well, including gender (early studies indicated the link was stronger in boys but recent findings are more contradictory), SES, parental psychopathology (e.g., ADHD or antisocial/criminal behavior), and caregiving environment (e.g., parental responsiveness) (Agrawal et al., 2010; Wakschlag et al., 2011).

Considerations for Prevention/Intervention

To prevent the negative effects of prenatal nicotine exposure on child development, women are advised to quit smoking before becoming pregnant. Once pregnant, smoking cessation should be done as early as possible to reduce impact on the developing fetus. Psychosocial support is an effective, evidence-based smoking cessation treatment for pregnant women, particularly if incentives are included. However, the safety and efficacy of pharmacotherapy during pregnancy (e.g., nicotine replacement therapy) remain unclear (Meernik & Goldstein, 2015).

For women who smoked during pregnancy, periodic developmental and behavioral assessment of their young children may identify early learning or behavioral problems requiring intervention. Parent training, behavior modification and wraparound

services that target multiple family risk factors may reduce externalizing behaviors, while medication management may be warranted if a child is formally diagnosed with an attention deficit disorder. Specific interventions that target self-regulatory skills may alter trajectories toward severe behavior problems in children with prenatal tobacco exposure (Wiebe et al., 2015). School accommodations for learning, attention and/or disruptive behaviors may also become necessary if problems persist in childhood and adolescence.

Prenatal Cocaine Exposure

Definitional Issues and Prevalence

Cocaine is one of the most commonly abused illicit drugs in the USA and Europe. During the "cocaine epidemic" in the USA of the late 1980s and early 1990s it was estimated that 50,000–100,000 children were born prenatally with cocaine exposure each year, with higher rates reported in urban areas (National Institute on Drug Abuse, 1996; Ostrea, Brady, Gause, Raymundo, & Stevens, 1992). Although the annual rate of affected births has dropped since then, it is currently estimated that nearly 7.5 million children have been affected by prenatal cocaine exposure (PCE) in the USA (Chae & Covington, 2009). Worldwide, 0.5–3 % of pregnant women are estimated to use cocaine (Lamy & Thibaut, 2010).

Cocaine use in expensive powder form became prevalent in the 1980s when portrayed as a "safe" drug by President Carter's drug "czar". By the 1990s, a cheap smokable "crack" form had been manufactured and epidemic use occurred in major urban areas, primarily by poor, minority men and women. Information on developmental outcomes comes primarily from a number of large prospective birth cohort studies initiated by the NIH in the early 1990s, and drug effects are confounded with the environmental risks associated with "crack" cocaine use in poor urban areas.

Impact on the Developing Child

Maternal cocaine use exposes the fetal brain to a powerful stimulant that readily crosses the fetal blood–brain barrier and can act directly to disrupt monoamine neurotransmitter systems important for directing fetal brain development (Kosofsky, Wilkins, Gressens, & Evrard, 1994; McCarthy, Kabir, Bhide, & Kosofsky, 2014) particularly in brain areas known to impact reward systems and executive function (McCarthy et al., 2014). Prenatal cocaine exposure can also act indirectly via its vasoconstrictive properties that limit oxygen and nutrition to the developing fetal brain (Smeriglio & Wilcox, 1999). A number of well-controlled prospective studies indicate that PCE affects fetal physical growth, resulting in an increased likelihood of preterm birth, low birth weight, shorter birth length, smaller head circumference, and growth retardation, an indication of potential developmental delay (Gouin,

Murphy, Shah, & Knowledge Synthesis Group on Determinants of Low Birth Weight and Preterm Births, 2011). Recent data suggest PCE is associated with persistent disruption in dopamine signaling, changes in pyramidal neuron dendritic structure, and fewer GABA neurons, all of which can compromise the dopamine-rich prefrontal cortex (McCarthy et al., 2014; Thompson, Levitt, & Stanwood, 2009). These structural brain differences may underlie cognitive deficits, including executive function, attention, and inhibitory control, in prenatally cocaine exposed children.

Brain imaging studies of cocaine-exposed children have consistently noted morphologic differences from non-exposed samples. These include less gray matter in the parietal and occipital lobes and lower volume of the corpus callosum in 7–8-year-olds (Singer et al., 2006), lower volume of the right anterior cerebellum at 11 years of age, and smaller caudate at adolescence (Avants et al., 2007).

Intellectual Functioning

Although global cognitive deficits have been noted in cohorts of children 1–3 years of age with PCE (Behnke, Smith, & Committee on Substance Abuse, & Committee on Fetus and Newborn, 2013; Richardson, Goldschmidt, & Willford, 2008; Singer et al., 2002), specific, rather than overall cognitive differences have been found in older children with PCE. School age PCE cohorts and comparison substance-exposed children had mean IQ scores between 0.5 and 1.0 SD below the mean, reflective of their poor urban environments, low SES, and elevated lead levels (Ackerman, Riggins, & Black, 2010).

Academic Functioning

PCE has not been directly associated with child academic achievement (Frank et al., 2005; Singer et al., 2008). However, PCE children were 2.8 times more likely to demonstrate learning disabilities than non-exposed peers at age 7 (Morrow et al., 2006) and to need individualized education plans and special support services (Levine et al., 2008) than non-exposed children. At 4 years, cocaine-exposed boys had deficits in arithmetic skills compared to non-exposed peers (Singer et al., 2004).

Neuropsychological Functioning

PCE appears to disrupt specific neuropsychological functions, including attention, executive function, and visual perceptual organization, especially difficulties with sustained (Bandstra, Morrow, Anthony, Accornero, & Fried, 2001) and selective (Savage, Brodsky, Malmud, Giannetta, & Hurt, 2005) attention. PCE children were more likely to demonstrate commission errors (Noland et al., 2005) at age 4, and omission errors and slower reaction times at ages 5–7 (Accornero, Anthony, Morrow, Xue, & Bandstra, 2006; Roth, Isquith, & Gioia, 2005).

Negative effects of PCE on EF have been found via experimental neuropsychological tasks during infancy (Noland et al., 2003) and on standard neuropsychological assessments at elementary school age (Eyler et al., 2009; Mayes, Molfese, Key, & Hunter, 2005) and at adolescence (Richardson, Goldschmidt, Larkby, & Day, 2015). In a study of inhibitory control using the Stroop interference task (Bridgett & Mayes, 2011), children with PCE made more errors than non-cocaine exposed (NCE) children at 7 years, but had more age related improvements between 7 and 12 years. While girls in both groups improved faster than boys, PCE girls did not catch up to their NCE peers.

Gender specific effects were also found in a study using parental ratings of EF that assessed functional aspects of school and home life. At 12 years, girls with PCE were rated by caregivers to have more problems in metacognition (planning/organizing and self-monitoring) but not behavioral regulation (Min et al., 2014a, Min, Minnes, Yoon, Short, & Singer, 2014b). In contrast, PCE effects were found in boys only using a computerized go/no-go task (Carmody, Bennett, & Lewis, 2011). Boys with heavier PCE showed deficits in attention and inhibitory behaviors at ages 6, 9, and 11. Negative effects of heavier PCE on inhibitory control at 8.5–11 years of age were found compared to lighter PCE and NCE (Rose-Jacobs et al., 2009), but no effects were noted at 12–14 years of age (Rose-Jacobs et al., 2011).

The Cleveland Prenatal Cocaine Study found that children with PCE had deficits on Perceptual Reasoning tasks from the Wechsler IQ tests at ages 4, 9, and 15 (Singer et al., 2004, 2008; Singer, Minnes, Min, Lewis, & Short, 2015). These IQ tasks of Block Design, Picture Arrangement, and Object Assembly measure nonverbal reasoning, visual-spatial processing, visual-perceptual organization, and the ability to learn new information.

Emotional and Behavioral Functioning

In the preschool years, studies provide conflicting evidence of PCE effects on behavior (Dixon, Kurtz, & Chin, 2008). However, findings on behavioral regulation converge at school age with few exceptions (Ackerman et al., 2010). PCE effects have been found on child-reported symptoms of Oppositional Defiant Disorder (ODD) and ADHD at 6 years (Linares et al., 2006), on caregiver-reported aggressive and delinquent behavior at 9 years (McLaughlin et al., 2011), on child-reported depressive symptoms and teacher-rated anxious/depressed behavior at 10 years (Richardson, Larkby, Goldschmidt, & Day, 2013), on teacher- and caregiver-rated externalizing behavior problems at 7, 9, and 11 years (Bada et al., 2011), and on child-reported externalizing behavior at 12 (Min, Minnes, Lang, et al., 2014a) and 15 years (Min, Minnes, Lang, et al., 2014a; Min, Minnes, Yoon, et al., 2014b; Richardson et al., 2013). Mixed findings of PCE by gender on behavioral adjustment have been noted, with PCE boys showing more clinically significant externalizing and delinquent behaviors using teacher ratings (Delaney-Black et al., 2000) and self-report (Bennett, Marini, Berzenski, Carmody, & Lewis, 2013) while other studies report effects of PCE in girls only (McLaughlin et al., 2011; Minnes et al.,

2010; Sood et al., 2005). The negative effects of PCE on externalizing behaviors have been consistent across ages with small effect sizes at 0.20 SD on average (Ackerman et al., 2010; Singer et al., 2015).

PCE effects have been noted in adolescence on substance use (Delaney-Black et al., 2011; Frank et al., 2011; Minnes et al., 2014; Richardson et al., 2013) and early sexual behavior (De Genna, Goldschmidt, & Richardson, 2014; Min, Minnes, Lang, Yoon, & Singer, 2015). PCE adolescents self-reported more substance use related problems at age 15, and were more likely to experience accidents, forgetfulness, and mood swings when using alcohol or drugs (Min, Minnes, Lang, et al., 2014a).

Language Functioning

Studies of language development in PCE children have also been consistent even after controlling for multiple prenatal and environmental confounders (Ackerman et al., 2010; Lambert & Bauer, 2012). The Miami Prenatal Cocaine study (Bandstra et al., 2011) reported a gradient (dose-dependent) relationship between PCE and lower receptive, expressive, and total language scores at 3, 5, and 12 years of age, with expressive language being most affected. Deficits in expressive language observed at age 3 years persisted to age 12 years. The Cleveland study (Lewis, Kirchner, et al., 2007; Singer et al., 2001) found stable negative effects of cocaine on expressive language skills across 1, 2, 4, and 6 years of age (Lewis, Fulton, et al., 2007; Lewis, Kirchner, et al., 2007). This cohort continued to show PCE-associated language deficits related to syntax and phonological awareness at age 10 (Lewis et al., 2011) and 12 years (Lewis et al., 2013). Gender differences were noted with PCE girls differentially affected at age 10, consistent with other research.

Specific Diagnostic Outcomes

Studies from two birth cohorts (Linares et al., 2006; Morrow et al., 2009) reported that ADHD and ODD were associated with prenatal cocaine exposure although these findings should be considered preliminary until replicated.

Prognosis and Moderating Factors

The net effect of PCE is in the range of small to medium effect sizes. Children prenatally exposed to cocaine are likely to continue to have functional deficits due to the teratogenic effects of PCE and from associated risk factors (low SES, caregivers' ongoing substance use, poor parenting, and violence exposure). Compromised development in language skills, neuropsychological functioning, and externalizing

behavior problems may lead to cascading effects in other developmental domains. As noted previously, gender may moderate PCE effects on behavior, but findings to date have been inconsistent.

Considerations for Prevention/Intervention

Interventions that provide stimulating, responsive caregiving may mitigate PCE effects in some aspects of development. In addition, drug treatment of maternal depressive symptoms during pregnancy may also mitigate harmful effects on the fetus (Singer et al., 2002; Singer, Salvator, et al., 2002). Preschool enrichment positively affected 4 year IQ in PCE children (Frank et al., 2005). A substantial (20–25 %) portion of PCE children from the Cleveland cohort placed in nonrelative foster-adoptive care had better quality home environments with lower lead levels, and caregivers with higher verbal skills and less depression than children with their biologic families. They also had better cognitive (Singer et al., 2004, 2008) and language (Lewis et al., 2011) outcomes compared to those in biological relative care through school age, that were positively correlated with the length of time in better caregiving environments (Singer et al., 2004). However, these protective effects were not found for behavioral outcomes (Linares et al., 2006; McLaughlin et al., 2011; Min, Minnes, Lang, et al., 2014a; Min, Minnes, Yoon, et al., 2014b; Minnes et al., 2010).

Amphetamines, Methamphetamine, and MDMA (3,4-Methylenedioxymethamphetamine)

Definitional Issues and Prevalence

Amphetamine and its related compounds are synthetic psychostimulants that resemble the neurotransmitter dopamine in chemical structure, accounting for their effects on the dopaminergic system. Amphetamine, methamphetamine, and 3,4, methylenedioxymethamphetamine (MDMA, “Ecstasy”) are highly similar, but not identical, psychostimulants. They cross the placenta to increase the levels of norepinephrine, dopamine, and serotonin in the synaptic cleft via transporter reuptake inhibition (Ross, Graham, Money, & Stanwood, 2015). Amphetamine is composed of two distinct compounds, dextroamphetamine and levoamphetamine, and medications containing amphetamine are prescribed for narcolepsy, obesity, ADHD, and Parkinson’s Disease. Prescription drugs containing amphetamine, such as Ritalin, Vyvanse, Adderall, and Concerta are frequently used by women of child bearing age with obesity and ADHD, but the prevalence of women using amphetamines for nonmedical reasons is currently unknown.

Methamphetamine and MDMA are illicit drugs that are part of the collective group of amphetamines. Substance Abuse and Mental Health Services Administration (2014) estimates that .3 % of adults age 18–25 reported using methamphetamine in the past month. The only study to assess methamphetamine prevalence in pregnant women found that 5 % of women in selected hospitals self-reported use in the US areas with significant overall use (Arria et al., 2006). Methamphetamine is more rapidly transported across the blood–brain barrier than amphetamine (Barr et al., 2006), with a higher potential for addiction.

MDMA, while similar to amphetamine, has additional hallucinogenic properties (Parrott, 2014) and a particular affinity for the serotonin transporter (Green, Mechan, Elliott, O'Shea, & Colado, 2003) in that 80 % of serotonin stores can be depleted in one episode. Usually taken in pill form, more recently MDMA has been popularized as "Molly", a powder form wrongly perceived as a safe form of the drug. MDMA has been called an "enactogen" referring to users' subjective experience of empathy, euphoria, and emotional warmth while using and has been used therapeutically to treat posttraumatic stress disorder.

MDMA is widely used recreationally throughout Europe, Australia, and the USA. Johnston et al. (2014) found 5.6 % of 12th graders in the USA reporting lifetime use of Ecstasy and Substance Abuse and Mental Health Services Administration (2014) reported 12.8 % of 18–25-year-olds with lifetime use. Amphetamine type stimulants have highest prevalence rates in New Zealand, Australia, and the western USA (Mohan, 2014). Their use has been increasing, moving eastward from epidemics first noted in the western and southwestern parts of the USA (Nordahl, Salo, & Leamon, 2003). Although effects of amphetamine type stimulants have been extensively studied in adults (Berman, Kuczenski, McCracken, & London, 2009; Nordahl et al., 2003; Parrott, 2014), the impact of prenatal exposure to these stimulants on child development has not been well documented.

Impact on the Developing Child

Given their similarities of action at the cellular level, the four major follow-up studies of prenatal amphetamine exposure will be summarized together. These studies include an early uncontrolled study from Sweden of growth and development of 65 children exposed to amphetamines through early adolescence (Billing, Eriksson, Larsson, & Zetterstrom, 1980). The New Zealand IDEAL study, a prospective, longitudinal, well-controlled study, has been following 100 methamphetamine-exposed children in comparison to similar non-exposed children since 2006 (Wouldes et al., 2014). The US IDEAL study recruited 204 methamphetamine-exposed and 208 non-exposed matched comparison children from four US sites (Los Angeles, CA; Des Moines, IA; Tulsa, OK; Honolulu, HI) and has followed them until 7.5 years old. The Drugs and Infancy Study (DAISY), a prospective longitudinal cohort design, followed 28 MDMA-exposed and 68 non-exposed infants from birth to 2

years of age using a volunteer sample of middle class recreational drug users from London, England. Infants were evaluated at 1, 4, 12, 18, and 24 months of age. The DAISY Study is the only available study worldwide to investigate prenatal MDMA exposure effects in humans (Moore et al., 2010).

Amphetamine exposure in pregnancy was associated with low birthweight and prematurity in one meta-analysis of ten small studies (Ladhani, Shah, Murphy, & Knowledge Synthesis Group on Determinants of Preterm/LBW Births, 2011). Several studies, including IDEAL, found that prenatal methamphetamine exposure was also related to prematurity, fetal growth retardation, and decreased birthweight, length, and head circumference (Smith et al., 2003). Methamphetamine-exposed infants appear to largely catch up in growth by 3 years of age. However, imaging studies indicated lower volume of the caudate nucleus and decreased cortical thickness at age 3 years in the same study (Zabaneh et al., 2012). In contrast, no differences were found in the DAISY study in birth complications or growth parameters, but MDMA exposure was associated with more male births, similar to findings of alterations in sex ratios seen with other toxins (Mocarelli et al., 2000; Singer, Moore, Fulton, et al., 2012a). One infant in the MDMA-exposed group in this study was diagnosed with Townes-Brocks Syndrome, a rare congenital anomaly that could not be attributed to MDMA exposure (Singer et al., 2012b). However, the finding is consistent with a study that found a 4–7 times higher risk of congenital malformations in a series of 136 MDMA-exposed pregnancies (McElhatton, Bateman, Evans, Pughe, & Thomas, 1999).

Structural brain abnormalities have been identified in children with prenatal methamphetamine exposure, i.e., regional brain volume reductions in the putamen, globus pallidus, hippocampus, and caudate and decreased cortical thickness (Chang et al., 2004), and lower apparent diffusion coefficient (ADC) in frontal and parietal white matter (Cloak, Ernst, Fujii, Hedemark, & Chang, 2009; Zabaneh et al., 2012). There are no similar studies of amphetamine or MDMA exposed infants.

Intellectual Functioning

Amphetamine-exposed children at age 4 had lower IQ scores, although in the average range of functioning, compared to a community sample in Sweden (Billing, Eriksson, Steneroth, & Zetterström, 1985). However, no differences in cognitive development related to methamphetamine exposure were found from 1–3 years of age on the Bayley Scales of Infant Development—Second Edition (BSID-II) relative to non-exposed children in the IDEAL Study through 7.5 years (Smith et al., 2011) nor in a small experimental study (Piper et al., 2011).

Similarly, no global differences on the MDI of the BSID-II between MDMA-exposed and non-exposed infants were found in the DAISY study. More heavily exposed infants achieved an MDI of 98.5±11 vs. 103.4±6 and 103.4±9 for lighter exposed and non-exposed. However, heavier MDMA exposure prenatally was predictive of a lower Mental Development Index score at 12 months only (Singer, Moore, Min, et al., 2012b) at an age when the MDI items are heavily dependent on motor skills.

Academic Functioning

Fifteen percent of 14–15-year-old amphetamine-exposed children were 1 year behind their school-age peers in the Swedish study, with problems in language and mathematics (Cernerud, Eriksson, Jonsson, Steneroth, & Zetterstrom, 1996) but there are no other reports on school achievement related to methamphetamine, MDMA, or amphetamine-exposed children.

Neuropsychological Functioning

The US IDEAL study identified lower grasping scores on the Peabody Developmental Motor Scales (PDMS-2) associated with heavier methamphetamine exposure from 1 to 3 years, but did not find a relationship with fine or gross motor skills on the Bayley Scales of Psychomotor Development Index (PDI) (Smith et al., 2011). Similar, but even more consistent motor deficits were found in MDMA-exposed infants in the DAISY study. At 4 months, MDMA-exposed infants were slower moving and more delayed as assessed by the motor subscale of the Behavioral Rating Scale (BRS) of the BSID-II, and more heavily exposed infants performed more poorly than comparison infants on the Alberta Infant Motor Scale (AIMS) (Singer, Moore, Fulton, et al., 2012a). By 12 months, significant delays in motor skills were identified for more heavily exposed MDMA infants on the BSID-II PDI and the BRS motor quality scale (Singer, Moore, Min, et al., 2012b). By 2 years, heavily MDMA-exposed infants still lagged behind the lighter and non-exposed comparison groups (Singer et al., 2015; Singer, Minnes, Min, Lewis, Lang, et al., 2015; Singer, Minnes, Min, Lewis, & Short, 2015).

Other specific deficits have been found related to methamphetamine exposure in preschool and early school age children. A subsample from the US IDEAL study was administered the Conner's Kiddie Continuous Performance Test (K-CPT) at age 5.5 years. While no differences were found in omission or commission errors or reaction time for correct trials, prenatal exposure was associated with outcomes predictive of ADHD. In a sample of 31, 7–9-year-old methamphetamine-exposed children compared to 35 non-exposed on the Conner's Parent Rating Scale at 7.5 years, exposed children were 2.8 times more likely to be rated to have cognitive problem scores above average. Parents rated their children to have more problems in executive function and the children were more likely to show poorer performance in spatial memory compared to non-exposed children (Roussotte et al., 2011).

Emotional and Behavioral Functioning

Aggressive behavior and poorer social functioning were related to the amount and duration of prenatal amphetamine exposure in the Swedish cohort at 8 years (Billing, Eriksson, Jonsson, Steneroth, & Zetterström, 1994). Likewise, in the US IDEAL study, higher emotional reactivity and more anxiety, depressive, and ADHD symptoms were

found at preschool age, but not at 7 1/2 years when using parent report (Smith et al., 2015). In the DAISY study, no effects of MDMA exposure were found on emotional regulation up to 2 years of age (Singer, Moore, Min, Goodwin, Turner, et al., 2015).

Impact on Other Areas of Functioning

The amphetamine exposed children in the Swedish cohort displayed deficits in math, language, and physical fitness activities at 14 years compared to normative groups (Cernerud et al., 1996), but no specific functional deficits have been noted in either the US or New Zealand IDEAL studies or the MDMA DAISY Study, although follow-up extends only from 2 to 7.5 years of age.

Specific Diagnostic Outcomes

Preschool outcomes in the US IDEAL Study suggested that ADHD was potentially related to methamphetamine exposure, a finding not replicated at early school age (Diaz et al., 2014).

Prognosis and Moderating Factors

The early identification of motor, executive function, and behavior regulation problems across these four cohorts raises concern about long-term school achievement and conduct problems in stimulant exposed children, although definitive outcomes await larger and longer term studies. As with cocaine and nicotine, environmental factors can either increase or decrease developmental risk. The IDEAL studies identified methamphetamine use to be associated with maternal psychiatric symptoms of paranoia, depression, suicidal ideation, and psychosis (Smith et al., 2015), problems that could be expected to affect child behavior. The Swedish cohort mothers had significant problems with alcoholism, also related to child outcomes (Billing, Eriksson, Steneroth, & Zetterstrom, 1988). In the DAISY study, no clinically significant differences in psychological distress symptoms in MDMA using women were noted although depressive symptoms were higher. These symptoms abated over the first year after infant birth coincident with decreased use of MDMA (Turner et al., 2014).

Considerations for Prevention/Intervention

Pregnant women should be apprised of the addictive potential of amphetamine type stimulants. Non-pharmacologic treatments for ADHD and weight control should be considered as first line interventions to prevent addiction. Treatment of depression,

alcohol and substance use prenatally may mitigate physiologic effects on the fetus and improve maternal–child interactions after birth. As motor delays can be identified early in development, and have been noted in the longitudinal studies, early screening and intervention for amphetamine-exposed infants is warranted.

Conclusion

Prenatal nicotine exposure is robustly associated with externalizing behavior problems and, to a lesser extent, compromised cognitive functioning and academic achievement and an increased risk of teen tobacco and other substance use. While the exact causal mechanisms of these associations are not yet determined in humans, the adverse effects of prenatal nicotine exposure persist on a long-term basis. Public health education efforts about the dangers of smoking during pregnancy are warranted. The increasing use among young people of alternative tobacco products perceived to be less harmful, such as e-cigarettes, smokeless tobacco, and hookahs, is an area of needed future research.

Prenatal cocaine exposure is associated with compromised language development, suboptimal executive functions, and greater externalizing behavior problems, as well as an increased risk of teen substance use and early sexual behavior, reflecting long-lasting teratogenic effects of PCE. Amphetamines are among the most poorly researched stimulants regarding use during pregnancy and impact on the developing child, despite their widespread legal and illegal use, with no controlled longitudinal studies beyond the preschool years. Limited data available suggest significant effects on brain development, behavioral adjustment, and motor skills, although the research literature is too small to allow firm conclusions to be drawn.

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