

## Prenatal cocaine exposure and child outcomes: a conference report based on a prospective study from Cleveland

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**Objective** The study aims to describe developmental outcomes from a longitudinal prospective cohort (Cleveland study) of prenatally cocaine-exposed (CE) infants.

**Methods** Two hundred eighteen CE and 197 nonexposed infants were enrolled at birth and followed through mid-adolescence. Birth CE status was determined by interview and biologic measures. Multiple demographic, drug, and environmental correlates were controlled. Standardized, normative, reliable measures of fetal growth, intelligence quotient (IQ), behavior, executive function, and language were given at each age and risk for substance misuse assessed in adolescence. A subset of children received volumetric magnetic resonance imaging (MRI) at 7 years and functional MRI at 14 years. The effect of CE was determined through multiple regression analyses controlling for confounders.

**Results** Cocaine exposed had significant negative effects on fetal growth, attention, executive function, language, and behavior, while overall IQ was not affected. CE had significant negative effects on perceptual reasoning IQ and visual–motor skills and predicted lower volume of corpus callosum and decreased gray matter in the occipital and parietal lobes. CE children had higher risk for substance misuse. Confounding risk factors had additive effects on developmental outcomes.

**Conclusions** Prenatal exposure to cocaine was related to poorer perceptual organization IQ, visual–spatial information processing, attention, language, executive function, and behavior regulation through early adolescence. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—cocaine; development; infant; adolescent; behavior; executive function

### INTRODUCTION

The use of the stimulant cocaine as a recreational drug has proliferated worldwide, with recent increasing use in Europe. The average prevalence of use was 1% in 2012 across Europe based on the United Nations World Drug Annual Report (2014), with Spain, the UK, Italy, and Ireland having the highest rates of use worldwide. Ten to fifteen per cent of 15–35 year olds in the UK are estimated to use cocaine. Because many users are women of child bearing age, concern has been raised regarding potential detrimental effects on pregnancy and child developmental outcomes. The occurrence of an epidemic in the 1980s and 1990s of cocaine use in its smokable or “crack” form in US cities, particularly in poor, urban centers, prompted nationwide alarm and the initiation of a number of National Institutes of

Health-funded studies to assess the effects of prenatal cocaine exposure on offspring development. This paper presents findings to date on child developmental outcomes from the Cleveland longitudinal cohort study that has been ongoing since 1994, with cohort findings through early adolescence (Minnes *et al.*, 2014b; Singer *et al.*, 2002a).

Cocaine is a powerful, addictive stimulant drug with well-defined medical and psychological effects on adults through its pharmacologic actions at different sites of neurotransmitter activity (Malanga and Kosofsky, 1999). Cocaine interferes with presynaptic catecholamine reuptake and activates the sympathetic nervous system to produce toxic effects of hypertension, tachycardia, vasoconstriction, and impairment of the sleep–wake cycle. Its strong impact on the dopamine system produces its euphoric and highly reinforcing effects. Several potential mechanisms for disruption of fetal development have been identified, including direct effects through defective synaptic development, hypoxemia through decreased uterine blood flow and oxygen deprivation, and vascular

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disruption affecting neuronal development (Benveniste *et al.*, 2010; Malanga and Kosofsky, 1999).

## METHODS

The Cleveland cohort consists of 218 cocaine-exposed (CE) and 197 nonexposed (NCE) infants and their mothers enrolled at birth with follow-up visits at 6, 12, and 24 months and 4, 6, 9, 10, 11, 12, 15, and 17 years. All participants were recruited from a high-risk screened population with exposure identified by self-report, urine, or meconium screen, with a comparison group from the same high-risk pool that was negative on all three drug measures.

A large number of confounding factors known to affect child outcomes were measured, as we wished to assess biologic drug effects controlling for other risk factors associated with drug use. Despite drawing from the same population, we found, as have other studies (Bada *et al.*, 2005; Eyler *et al.*, 1998; Frank *et al.*, 2001), that cocaine using women were older, had more children, had less prenatal care, were less likely to be married, had lower IQ, and were more likely to use large amounts of alcohol, marijuana, and tobacco while pregnant. They were also primarily of low socioeconomic status (SES), more likely to be psychologically distressed, and of minority race. Thus, these factors have been controlled in all data analyses. Women, on average, used 25 “rocks” of cocaine a week, with use of all substances declining over pregnancy trimesters (refer to Singer *et al.*, 2002b for full details of recruitment, assessment, and drug use). To date, cohort retention has been excellent at 89% or greater for all follow-up visits.

## RESULTS

From birth, there were significant neurotoxic effects of cocaine exposure independent of other drugs or confounding factors. Fetal growth deficiencies in head circumference, length, and weight signaled prenatal physiologic effects (Singer *et al.*, 2002b) and are characteristic of the majority of studies of CE infants (Bada *et al.*, 2005; Frank *et al.*, 2001). In a separate sample of very low birthweight (<1500 g) infants, we found CE infants to have a higher incidence of intraventricular hemorrhage (Singer *et al.*, 1994) likely related to maternal cardiovascular effects.

Neonatal neurobehavioral abnormalities were also evident on standardized exams with the more heavily exposed CE infants exhibiting poorer visual attention, jitteriness, and a higher likelihood of motor and tone abnormalities than the comparison group (Singer

*et al.*, 2000), suggesting early self-regulatory problems. Visual attention and discrimination were also deficient in the neonatal period as measured by an assessment of the neonate's established preference for face-like stimuli (Singer *et al.*, 1999), consistent with findings from another cohort study (Coles *et al.*, 1999). These neurobehavioral deficits were also visible in the CE infants' interactions with their caregivers, in which they were rated as being less clear in their signals to the caregiver (Minnes *et al.*, 2005).

At all follow-up ages in this cohort from birth to 15 years, we have found consistent deficits related to CE on a number of important developmental domains, primarily attention, language, perceptual organization, and executive function, as well as behavioral outcomes and risk for substance misuse or abuse. By 2 years of age, overall mental, but not motor, developmental outcomes were delayed on standardized testing and mediated by the lower head circumference, an indicator of brain growth, of CE children at birth (Singer *et al.*, 2002a). Several other longitudinal cohort investigations have also found such generalized delays at 2 and 3 years (Behnke *et al.*, 2006; Messinger *et al.*, 2004; Richardson *et al.*, 2008).

Language delays were apparent in the more heavily exposed CE group as early as 12 months of age and were strongly related to poorer attention and auditory comprehension on the Preschool Language Scales (Singer *et al.*, 2001). Several other tasks differentiated CE infants from comparison infants from 6 to 12 months of age. At 6 months of age, CE infants had poorer performance and were more likely to be classified “at risk” (27 vs 17%,  $p < .05$ ) on the Fagan Test of Infant Intelligence, a test of cognition and recognition memory dependent on visual attention and discrimination skills (Singer *et al.*, 2005), replicating similar findings by Jacobson and Jacobson, 1996 (Jacobson *et al.*, 1996). At 12 months, heavily exposed CE infants performed more poorly on the A-not-B test that measures early executive function dependent on visual attention, memory, and comprehension of object permanence (Noland *et al.*, 2003). Visual-motor tasks have been noted to be particularly affected by prenatal cocaine exposure in other cohorts as well (Bennett *et al.*, 2008; Mayes *et al.*, 2007).

Our studies Singer *et al.*, 2001; (Lewis *et al.*, 2004; Lewis *et al.*, 2007; Lewis *et al.*, 2011; Lewis *et al.*, 2013) found a stable language skill deficit over time in this cohort from 1 to 6 years of age. At 4 years, the CE group performed more poorly on expressive language and total language scores (Lewis *et al.*, 2004) and on a selective attention task (Noland *et al.*, 2005). When more specific deficits could be measured at older ages, CE

children performed more poorly on discrete language tasks of phonological awareness, sentence combining, and malapropisms at 10 years (Lewis *et al.*, 2011) and comparable phonologic processing tests at 12 years (Lewis *et al.*, 2013). A core underlying skill for these functions is auditory comprehension, first noted to be delayed in the CE group at 1 year of age (Singer *et al.*, 2001). These findings are consistent with those of another large cohort of CE infants (Bandstra *et al.*, 2011).

Poorer performance on the perceptual reasoning IQ of the Wechsler Intelligence Scale for Children III was noted at 9 years of age (Singer *et al.*, 2008) and persisted to 15 years (Singer *et al.*, 2014) indicating CE effects on nonverbal reasoning, visual-spatial processing, visual-perceptual organizational skills, and the ability to learn new information. Tests comprising the perceptual reasoning IQ at 9 and 15 years are older age versions of the visual-motor tasks of Block Design and Object Assembly that were found to be lagging in CE children at 4 years, in a dose-dependent manner (Singer *et al.*, 2004) on the preschool version of the Wechsler IQ test. A similar dose-response relationship was found at 9 years between the amount and duration of prenatal cocaine exposure and attenuation of perceptual reasoning IQ (Singer *et al.*, 2008). These findings were congruent with structural brain imaging results at 7–8 years in matched subgroups of CE and NCE children from the cohort that showed lower volumes of the corpus callosum and less gray matter in the left occipital and right parietal lobes, areas implicated in visual functioning and language processing (Singer *et al.*, 2006). An additional connection with underlying brain functioning between prenatal cocaine exposure and brain activation in 26 adolescents from this cohort was also found at 14 years of age using a novel functional magnetic resonance imaging Block Design task based on the Wechsler Intelligence Scale for Children III Block Design task that differentiated CE children at 4, 9, and 15 years noted previously. CE children showed reduced activation in brain areas of the visual cortex supporting visual processing and implicated in the analysis of visual form, motion, and object representation (Minnes *et al.*, 2011). Of interest, using another visual-perceptual executive functioning task, the Stroop Test, similar deficits were noted in two other CE cohorts at school age (Mayes *et al.*, 2007; Rose-jacobs *et al.*, 2009).

Because evidence of cocaine's early disruption of neurotransmitter systems (Mayes, 2002; Stanwood *et al.*, 2001) raised concerns about the development of self-regulatory behavior, CE children have been considered at risk for behavioral, mental health, and substance misuse or abuse problems, areas that have

been examined in a number of cohorts including the Cleveland cohort. In our studies, both self-report and caregiver-rated measures have been utilized, with self-report measures at 6 Linares *et al.* (2006), 9 (Mclaughlin *et al.*, 2011), and 12–15 years (Min *et al.*, 2014a). At 6 years (Linares *et al.*, 2006), CE children rated themselves as having more attentional problems and more oppositional defiant symptoms than NCE children, but they did not report these symptoms at 9 years (Mclaughlin *et al.*, 2011). Using a different self-report measure at 12–15 years, CE children rated themselves as having more externalizing problems, with greater effects related to heavier exposure (Min *et al.*, 2014a; Min *et al.*, 2014b).

Caregiver-rated measures of the cohort yielded somewhat different findings. At 6 years, CE children in adoptive or foster care were rated as having more aggression, social, thought, and attention problems and delinquent behaviors than CE children in birth or kinship homes or NCE children (Linares *et al.*, 2006). At 9 years, CE children were rated as more aggressive, and CE girls were rated as displaying more delinquent behaviors than NCE children (Mclaughlin *et al.*, 2011), an effect also seen in a longitudinal analysis from 4–10 years (Minnes *et al.*, 2010). In addition, the same effect of foster or adoptive caregivers perceiving their CE children to have more attentional problems and externalizing behaviors than nonexposed children or CE children in kinship care was also evident at 9 years (Mclaughlin *et al.*, 2011).

Some discussion regarding the use of caregiver-rated measures for CE children is warranted, given the well-established relationship of caregiver-rated measures to caregiver IQ, education, and depressive symptoms. While all of these factors were controlled in data analyses, it is not possible to discriminate whether foster or adoptive caregivers were especially concerned about or observant of their CE children and thus more likely to rate them as more problematic or whether their perceptions were, in fact, realistic appraisals of children who had greater cocaine exposure prenatally and subsequently more behavioral problems (Minnes *et al.*, 2008; Singer *et al.*, 2004). However, our overall findings of an increase in externalizing behaviors in CE children have been found in other cohorts (Bada *et al.*, 2007; Delaney-black *et al.*, 2004; Lester *et al.*, 2009). Gender findings remain quite mixed, with some studies finding greater effects in boys (Bennett *et al.*, 2008), while the Cleveland cohort has seen greater effects in girls.

Consistent with earlier assessments of executive function at 12 years, heavy prenatal exposure was associated with more difficulty with planning,

organizing, and monitoring behavior via caregiver report. Heavier CE exposure was associated with problems initiating, with working memory, and with organization of materials only for girls (Minnes *et al.*, 2014c). CE adolescents at 15 years described themselves overall as having more problems in inhibiting behavior than NCE adolescents. Neuropsychological assessment indicated that CE girls were less efficient than NCE girls in solving a planning task, another indicator of executive function (Minnes *et al.*, 2014a).

A major issue of interest is in understanding the role of prenatal drug exposure and later substance abuse risk. CE adolescents self-reported that they were more likely to use alcohol, tobacco, and/or marijuana by age 15 compared with NCE adolescents (Minnes *et al.*, 2014c). They were also at greater risk for substance-use-related problems than NCE adolescents and were more likely to describe experiencing accidents, feelings of addiction, forgetfulness, and mood swings when using alcohol or drugs (Min *et al.*, 2014a). Similarly, CE was associated with initiation of any substance use in adolescence in two other large cohorts (Frank *et al.*, 2011; Richardson *et al.*, 2013).

## DISCUSSION

This paper summarizes findings from the ongoing study of the Cleveland, Ohio, cohort in the USA that has, to date, followed cocaine, polydrug-exposed infants from birth to mid adolescence, investigating cognitive, language, neuropsychological, and behavioral functioning, with control for multiple confounding factors. Prenatal cocaine exposure had significant low to moderate effects on fetal growth, attention, language, visual-motor perceptual organization, executive function, externalizing behavior problems, and risk for substance misuse, controlling for multiple confounding factors. Confounding drug and environmental factors also had significant effects on child outcomes, especially alcohol and tobacco exposure, lead exposure, maternal/caregiver education, IQ, and depression, the quality of the caregiving environment, and violence exposure, all of which had additive effects. Thus, many children had multiple risk factors, and CE exposure added to the effects of these risk factors.

The large sample size of this cohort, exceptional retention rate, longitudinal prospective design, careful measurement with biologic and maternal report of prenatal drug exposure, and assessment of a large number of confounding variables, including lead exposure, enhance confidence in the findings. Nevertheless, these

findings may not be generalizable beyond the low-SES, urban, population of the cohort, characteristic of the majority of US cohorts.

## CONCLUSIONS

Continued studies into adulthood will help determine whether the neuropsychological, cognitive, and language deficits related to CE, as well as the early indications of behavioral and substance use risk, persist through early adulthood and affect social and vocational adjustment. Thus, continued follow-up is important.

Given the homogeneous composition of most US cohorts with restriction to lower SES groups, future studies focused on the growing recreational users in Europe would enhance understanding of the effects of prenatal cocaine exposure in populations without environmental risk factors associated with low SES.

## CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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