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Prenatal methamphetamine exposure and neurodevelopmental outcomes in children from 1 to 3 years

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ABSTRACT

Background: Despite the evidence that women world-wide are using methamphetamine (MA) during pregnancy little is known about the neurodevelopment of their children.
Design: The controlled, prospective longitudinal New Zealand (NZ) Infant Development, Environment and Lifestyle (IDEAL) study was carried out in Auckland, NZ. Participants were 103 children exposed to MA prenatally and 107 who were not exposed. The Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI) of the Bayley Scales of Infant Development, Second Edition (BSID-II) measured cognitive and motor performances at ages 1, 2 and 3, and the Peabody Developmental Motor Scale, Second Edition (PDMS-II) measured gross and fine motor performances at 1 and 3. Measures of the child's environment included the Home Observation of Measurement of the Environment and the Maternal Lifestyle Interview. The Substance Use Inventory measured maternal drug use.
Results: After controlling for other drug use and contextual factors, prenatal MA exposure was associated with poorer motor performance at 1 and 2 years on the BSID-II. No differences were observed for cognitive development (MDI). Relative to non-MA exposed children, longitudinal scores on the PDI and the gross motor scale of the PDMS-2 were 4.3 and 3.2 points lower, respectively. Being male and of Maori descent predicted lower cognitive scores (MDI) and being male predicted lower fine motor scores (PDMS-2).
Conclusions: Prenatal exposure to MA was associated with delayed gross motor development over the first 3 years, but not with cognitive development. However, being male and of Maori descent were both associated with poorer cognitive outcomes. Males in general did more poorly on tasks related to fine motor development.

1. Introduction

Amphetamine-type stimulants (ATS) are the second most widely used illicit drug, after marijuana with an estimated prevalence of 0.3–1.2% in 2010, or between 14 and 52.5 million global users (UNODC, 2012). International trends of ATS show an increase in their initiation of use in the United States (US), East Asia and Oceania (UNODC, 2010, 2011). Oceania is the region with the highest prevalence of ATS use with New Zealand (NZ) having the second highest annual estimate (2.1%) after Australia (2.7%) (UNODC, 2011). Methamphetamine (MA) is a particularly potent form of ATS and reports suggest that a substantial number of women are using it during pregnancy resulting in an escalation of women seeking treatment for prenatal MA dependence (Arria et al., 2006; Substance Abuse and Mental Health Services Administration, 2011; Wouldes et al., 2004).

MA is a CNS stimulant that acts predominantly on the sympathetic nervous system. Acute administration of MA causes the release of monoamines dopamine, serotonin and norepinephrine. The psychoactive and potential neurotoxic effects from prolonged or high doses of MA may occur due to the following mechanisms that increase the synaptic or extracellular levels of these monoamines, primarily dopamine: 1) displacement of monoamines from synaptic vesicles to the cytosol; 2) reverse transport of neurotransmitters through plasma membrane transporters and through blocking the activity of dopamine transporters as well as decreasing the expression of these transporters at the cell surface; 3) increased activity and expression of tyrosine hydroxylase; and 4) inhibition of monoamine oxidase (Nordahl et al., 2003; Panenka et al., 2013; Rothman et al., 2001; Scott et al., 2007).

Preclinical studies have shown MA to be neurotoxic to mature dopaminergic and serotonergic axons and terminal arbors and possibly glutaminergic axons through the production of reactive oxygen species

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and nitric oxide, p53 activation resulting in cell death and mitochondrial dysfunction (Quinton and Yamamoto, 2006). The neurotoxicity of MA on the developing brain is not well understood, however, given the widespread influence of dopaminergic, serotonergic and glutaminergic systems on neuronal growth and connectivity, prenatal exposure may directly alter developing neural circuitry. Additionally, neurotoxic effects could occur indirectly through maternal anorexic effects of MA, through vasoconstrictive effects resulting in reduced uteroplacental blood flow and fetal hypoxia or through a cascade of events that repeatedly challenge the stress-response systems during gestation leading to an alteration in the hypothalamic–pituitary–adrenal axis (Lester and Padbury, 2009; Salisbury et al., 2009; Stek et al., 1993).

Evidence from animal studies have revealed that prenatal administration of MA is toxic to dopaminergic and serotonergic neurons (Fuller and Hemrick-Luecke, 1992; Pu and Voorhees, 1993); and results in motor and learning impairment (Itoh et al., 1991; Slamberova et al., 2005; Wallace et al., 1999). Prenatal exposure in mice has been found to enhance conceptual DNA oxidation and lead to long-term and possibly permanent postnatal neurodevelopmental deficits in motor coordination (Jeng et al., 2005). Deficits originated from a single exposure to MA during either the embryonic period of organogenesis or the later fetal period of functional development suggesting a broad window of risk during gestation. Brain imaging studies of MA exposed children have shown aberrant neuronal and glial development and volumetric differences in subcortical brain regions that were related to inhibitory behavior, working memory, sustained attention and visual motor integration, and verbal and memory tasks (Chang et al., 2004, 2009; Cloak et al., 2009). A more recent study identified increased cortical thickness in perisylvian and orbital-frontal cortices; and reduced caudate nucleus volumes that were associated with deficits in attention in MA exposed children between 3 and 5 years of age (Derauf et al., 2012).

For children exposed prenatally to MA, there may be early and ongoing deficits in neurodevelopment. At present the only evidence of the long-term effects of prenatal exposure to any ATS comes from an early study in Sweden that has followed the growth and development of 65 children exposed prenatally to amphetamine (Billing et al., 1980, 1985, 1988, 1994; Cernerud et al., 1996; Eriksson et al., 1978, 1979, 1981, 1994). Results using the Terman Merrill method of developmental screening showed the amphetamine exposed children at age four had lower IQ scores (103 vs 110, respectively) and more "problem children" than an unselected community sample of Swedish children (Billing et al., 1985). However, maternal alcohol and substance abuse during pregnancy was correlated negatively with the child's adjustment as were numbers of paternal criminal convictions, number of maternal stress factors and number of earlier children born to the mother (Billing et al., 1988). Reports from this prospective study also found an association between the amount and duration of prenatal amphetamine exposure and aggressive behavior, social adjustment and psychometric assessments at age 8. Alcohol abuse and attitude toward the pregnancy were also significantly correlated with these outcomes (Eriksson et al., 1989) (Billing et al., 1994). At ages 14–15 exposed children performed more poorly on tests on Swedish language, math and physical training than their schoolmates and 15% were one year behind for their age (Cernerud et al., 1996; Eriksson et al., 2000). As in earlier reports maternal alcohol abuse was correlated with one of the primary outcomes, Swedish language scores (Cernerud et al., 1996). The lack of a control group and the association of other environmental factors associated with the developmental outcomes of these amphetamine exposed children make it difficult to determine whether these outcomes are due to the direct effects of prenatal exposure to amphetamine and/or alcohol, or the indirect effects of maternal factors and the postnatal environment.

Emerging evidence from the only current well-controlled, prospective, longitudinal studies of prenatal MA use, the US and NZ Infant Development, Environment and Lifestyle (IDEAL) studies, have found linkages between prenatal MA exposure and poorer quality of movement, more total stress/abstinence, physiological stress, and CNS stress in newborns of the US and NZ samples (LaGasse et al., 2011; Smith et al., 2008), and more non-optimal reflexes in the NZ sample. Relevant to this report, the US IDEAL study found a lower grasping score on the Peabody Developmental Motor Scales-II (PDMS-II) at age 1, that persisted in longitudinal models through age 3 (Smith et al., 2011). The impact of prenatal MA exposure on neurodevelopment may also be inferred from a longitudinal study of another ATS, 3,4-methylenedioxymethamine (MDMA) carried out in the United Kingdom (UK) (Singer et al., 2012a). Similar to the US IDEAL findings, early reports from the UK study revealed an association between prenatal exposure to MDMA and lower quality of movement and less mature gross motor functioning at age 4 months and 1 year (Singer et al., 2012a, 2012b).

Increased psychosocial problems, multiple drug use and mental health problems are common among women who use illicit drugs (Arria et al., 2006; Bjorn and Kesmodel, 2011; Richardson et al., 1995; Wouldes et al., 2013; Wouldes and Woodward, 2010). Therefore, any conclusions concerning the direct effects of prenatal MA exposure on neurodevelopment must also consider the context of the home environment and a wide range of potentially confounding maternal lifestyle factors.

The specific aims of this investigation were the following: first, to describe and compare the cognitive and motor development at 1, 2 and 3 years of age in a sample of NZ children exposed prenatally to MA with a matched, non-MA exposed group of children; second, to determine the extent of change in cognitive and motor development in MA-exposed children relative to non-MA exposed children over these 3 years using longitudinal analytic techniques that control for other drug use prenatally, birth outcomes, the ensuing home environment, and maternal characteristics and lifestyle factors.

2. Methods

2.1. Sample

Recruitment occurred between 2006 and 2010 through referrals from maternity services at participating hospitals and independent midwife practices. Screening through midwives in these services determined whether the mother met the study criteria. If the mother met the criteria and agreed to learn more about the study, study staff met with her to explain the study in detail and obtain written consent to participate. Trained interviewers reviewed the study protocol again with the mother post-partum, prior to discharge, to affirm consent, collect meconium from her infant, and obtain substance use and lifestyle information. Study approval was obtained from the following: Auckland and Waitemata District Health Boards and their Māori ethics committees, and the NZ Ministry of Health's Northern Regional Ethics Committee. Confidentiality around maternal substance use was established according to the NZ Ministry of Health Ethics Committee guidelines. Consistent with these guidelines, any evidence of child abuse or neglect would require referral to Child Youth and Family Protective Services, but there is no mandatory reporting of MA use during pregnancy.

Maternal exclusion criteria were: prenatal use of hallucinogens; history of intellectual disability; overt psychotic behavior or a documented history of psychosis; non-English speaking (except Māori); multiple gestation; newborn critically ill and unlikely to survive at birth or born with a chromosomal disorder; previous child already enrolled in the study, and mother <17.5 years of age at the infant's birth. MA exposure was determined by maternal self-report of any MA use during the current pregnancy or MA detected in her infant's meconium by gas chromatography–mass spectrometry. Comparison mothers required *both* maternal denial of MA use during pregnancy *and* a negative meconium result for MA or other stimulants. Comparisons were also excluded if their infant's meconium screened positive for cocaine or opiates or if they reported use of cocaine or opiates. Of the 103 participants