Developmental outcomes of 3,4-methylenedioxymethamphetamine (ecstasy)-exposed infants in the UK

Lynn T. Singer1,*, Derek G. Moore2, Meeyoung O. Min1, Julia Goodwin2, John J. D. Turner2, Sarah Fulton1, and Andrew C. Parrott3
1Case Western Reserve University, Cleveland, Ohio, USA
2The University of East London, London, UK
3Swansea University, Swansea, UK

Abstract

Objective—This paper aims to review findings from a longitudinal study of prenatal methylenedioxymethamphetamine (MDMA, “ecstasy”) on infant development.

Methods—In a prospective, longitudinal cohort design, we followed 28 MDMA-exposed and 68 non-MDMA-exposed infants from birth to 2 years of age. Women recruited voluntarily into a study of recreational drug use during pregnancy were interviewed to obtain type, frequency, and amount of recreational drug use. Their children were followed for a 2-year period after birth. A large number of drug and environmental covariates were controlled. Infants were seen at 1, 4, 12, 18, and 24 months using standardized normative tests of mental and motor development.

Results—There were no differences between MDMA-exposed and non-MDMA-exposed infants at birth except that MDMA-exposed infants were more likely to be male. Motor delays were evident in MDMA infants at each age and amount of MDMA exposure predicted motor deficits at 12 months in a dose-dependent fashion.

Conclusions—Prenatal MDMA exposure is related to fine and gross motor delays in the first 2 years of life. Follow-up studies are needed to determine long-term effects.

Keywords

MDMA; ecstasy; methylenedioxymethamphetamine; infant development; prenatal; motor

*Correspondence to: L. T. Singer, PhD, Case Western Reserve University, Adelbert Hall, Room 216, 2040 Adelbert Road, Cleveland, Ohio 44106, USA. Tel: 01(216) 368-4389; Fax: 01(216) 368-4325 Lynn.Singer@case.edu.

CONFLICT OF INTEREST
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INTRODUCTION

Recreational use of stimulant drugs is now widespread worldwide, especially in the Americas, Europe, Japan, Australia, and New Zealand and particularly among young adults aged 18–34 years (Carvalho et al., 2012; Cruickshank and Dyer, 2009; Feyissa and Kelly, 2008; Panenka et al., 2013; Parrott, 2013a; Parrott, 2014—submitted). Because of greater social acceptability and changing gender and social mores, many users are women of childbearing age (McElhatton et al., 1999; Degenhardt et al., 2010). Numerous studies have documented the physical and mental health effects of stimulant drug use in adults (see the aforementioned reviews). However, there are relatively few studies of the effects of recreational stimulant drugs on offspring who have been prenatally exposed, as these studies are costly, require long-term tracking and follow-up, and are methodologically complex. In this paper, we present a review of findings from such a study. This was a longitudinal cohort study of infants prenatally exposed to 3,4-methylenedioxymethamphetamine, MDMA or “ecstasy” in the UK.

3,4-Methylenedioxymethamphetamine is a widely used, illicit recreational drug, especially among young adults (Parrott, 2013b; Turner et al., 2014). MDMA is a powerful, indirect monoaminergic agonist that both inhibits the reuptake and promotes the release of serotonin (5-HT) and dopamine (Green et al., 2003), affecting physiological and psychological functions. Previous studies (Singer et al., 2004; Parrott et al., 2014) uncovered a wide range of psychological effects in adult ecstasy users, suggesting that fetal exposure may affect serotonergic functioning across the central nervous system and negatively affect those functions subserved by serotonin (McCann et al., 2008; Kish et al., 2010; Parrott, 2013b). A range of maternal effects from MDMA use during pregnancy may also affect the fetus, including physiological overstimulation, hyperthermia, increased cortisol levels, and post-use depression, sleep impairment, and decreased appetite (Parrott et al., 2014). In addition, animal studies have found prenatal MDMA exposure to be related to long-term memory and learning impairments (Piper, 2007; Skelton et al., 2008). Further, a UK Teratology Services Information study found a four to seven times higher risk of congenital malformations in 136 MDMA-exposed pregnancies (McElhatton et al., 1999).

A strong conceptual framework for prenatal drug exposure studies can be found in neurobehavioral teratology, the study of the causes of abnormalities in behavioral and physiologic development from toxic or environmental factors. The developing fetus is highly vulnerable to agents that have negligible or nontoxic effects in adults, and toxic exposure can cause a range of effects (Riley and Vorhees, 1986). To date, there have been no human studies of the developmental outcomes of infants exposed prenatally to MDMA. We report on the findings from the first study to investigate patterns of use of MDMA-using women during pregnancy and to assess child developmental outcomes until the age of 2 years. We hypothesized that MDMA infants would perform more poorly than nonexposed infants on developmental outcomes after controlling for other drugs and relevant confounders.
METHODS

The Drugs and Infancy Study was funded by the US National Institute on Drug Abuse as a collaborative effort of the University of East London and Case Western Reserve University in Cleveland, Ohio. This prospective study, funded from 2001 to 2005, monitored self-reported recreational drug users of MDMA, tobacco, cannabis, alcohol, and cocaine during pregnancy in the UK with a focus on assessing patterns of use and developmental effects of MDMA on offspring (Moore et al., 2010).

Participants were volunteers who responded to nurse midwives or to advertisements requesting participation in a study of recreational drug use in pregnancy, listing ecstasy, tobacco, cannabis, alcohol, and cocaine as examples. Women with positive HIV status, significant intellectual disability (IQ <70), or severe known psychiatric or medical illness were excluded as were infants with diagnosable illness at birth.

Ninety-six (28 MDMA and 68 non-MDMA) women were recruited by the University of East London staff through midwives, leaflets in prenatal clinics, or advertisements in pregnancy magazines to participate in a study of recreational drug use during pregnancy (details of recruitment, exclusion, and participation can be found in Moore et al., 2010, and Moore et al., 2011). MDMA status was determined by maternal interview on three occasions during pregnancy or after birth and information on frequency, amount, and duration of use before and after pregnancy obtained for MDMA and other drugs. To obtain drug use patterns, trained researchers interviewed women/mothers at home or in a private room at the university or, in a few cases, by phone. The interview was an adaptation of the interview for a US cocaine exposure study (Singer et al., 2002) that added questions related to substances commonly used in the UK and comprised three parts: (i) lifetime use; (ii) use in the month prior to pregnancy and the first two trimesters; and (iii) use in the third trimester (see Moore et al., 2011, for details).

Infants were evaluated at 1, 4, 12, 18, and 24 months of age with the Bayley Scales of Infant Development, including the Mental (Mental Development Index (MDI)), Motor (Psychomotor Development Index (PDI)), and Behavioral Rating Scales (BRS) (Bayley, 1993) by examiners blinded to infant drug status. At 1 month, infants were administered the Neonatal Intensive Care Unit Network Neurobehavioral Scales (Lester and Tronick, 2004). At 4 and 12 months, the Alberta Infant Motor Scales (Piper et al., 1992) and, at 12 months, the Preschool Language Scales (Zimmerman et al., 1992) were given. To control for confounding factors known to be related to child outcomes that are frequently associated with drug use, all mothers were assessed for psychological distress symptoms using the Brief Symptom Inventory (Derogatis, 1992), and for addiction severity with the Drug Abuse Screening Test (Skinner, 1982). Intellectual ability was measured through two subscales of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Maternal age, years of education, marital and employment status, income, socioeconomic status, and parity were also obtained. At each visit, maternal postpartum drug use was assessed, and the quality of the caregiving environment was evaluated with the Home Observation for Measurement of the Environment Inventory. All child examiners were masked to MDMA status.
To assess the effects of MDMA, both two-group (MDMA versus non-MDMA) and three-group status (heavier versus lighter MDMA versus non-MDMA) comparisons were evaluated at each age controlling for significant covariates. For a longitudinal assessment of effects of MDMA over time on Bayley outcomes, a mixed linear model approach with maximum likelihood estimation procedures was used. Covariates related to both outcomes and MDMA use at \( p < 0.2 \) were evaluated and retained if significant at \( p < 0.10 \) in the regression model. Gender effects were also examined.

**RESULTS**

Women in this sample were, on average, 29 years of age, primarily white (85%), married or partnered (82%), had some university education, and were of largely middle socioeconomic status and of average intelligence. There were no differences between MDMA-using and non-MDMA-using women on any parameter except that women in the MDMA group had fewer children. The majority of women in both groups were polydrug users up to and during pregnancy, primarily using tobacco, cannabis, and alcohol (Moore et al., 2010).

Methylenedioxymethamphetamine users were divided into heavier (\( n = 13 \)) and lighter (\( n = 15 \)) groups based on a median split of the total number of tablets taken averaged over the pregnancy. Heavier users averaged 1.3 (1.4) tablets in total over the three trimesters and 1 month prior to pregnancy compared with 0.07 (0.04) for lighter users. The amount of drugs used during pregnancy decreased over the trimesters for all women with use of cannabis most likely to persist if at all (see Moore et al., 2010). Only one woman reported using MDMA in the third trimester (Moore et al., 2010; Singer et al., 2012a).

**CHILD OUTCOMES**

3,4-Methylenedioxymethamphetamine-exposed infants did not differ from non-MDMA-exposed infants on any birth parameter including birthweight, prematurity, length, or gestational age, except that the MDMA group was more likely to be male, 71% vs. 46%; O.R. (Odds Ratio) = 3.2, 95% confidence interval: 1.2–8.2, \( p < 0.02 \). One child in the MDMA group was diagnosed with Townes–Brocks syndrome, a rare genetic malformation (Powell and Michaelis, 1999). Inclusion or exclusion of this child from comparisons did not affect results of any statistical analysis.

Comparison of Neonatal Intensive Care Unit Network Neurobehavioral Scales outcomes in the neonatal period yielded no significant differences between exposed and nonexposed groups although there were nonsignificant trends for exposed infants to be more lethargic (91% vs. 73%, \( X^2 = 3.3, p < 0.069 \)) and less hypertonc (9% vs. 27%, \( X^2 = 3.3, p < 0.069 \)) (Singer et al., 2012a).

At 4, 12, 18, and 24 months, there were no differences on the Preschool Language Scale or the Attention, Arousal, Orientation, and Emotional Regulation subscales of the BRS. However, at 4 months, MDMA-exposed infants had slower and more delayed movements as assessed by the BRS, and more heavily exposed infants performed less well on the Alberta Infant Motor Scales (AIMS). Mean percentile scores were 35.1 ± 24 for the heavier MDMA
group versus 65.7 ± 23 and 45.9 ± 28 for the lighter MDMA and nonexposed groups, \( p < 0.03 \) (Singer et al., 2012a), on the AIMS.

At 12 months, motor deficits in the MDMA group were even more pronounced, with PDI mean scores of 92.0 ± 16 and 99.8 ± 12 in the none and lighter groups, respectively, versus 76 ± 12 for the more heavily exposed MDMA group (\( F = 10.7, p < 0.002 \)), compared with an average standard score of 100. These delays were also reflected in the examiner-rated RRS motor quality scale. Heavier MDMA-exposed infants were rated more poorly in motor quality than lighter or nonexposed infants on the Motor Quality Scale at percentile 71.3 (32) vs. 88.8 (15) and 87.6 (17), respectively, \( F = 12.4, p < 0.001 \) (Singer et al., 2012a). At 12 months, the amount of prenatal MDMA exposure predicted lower MDI scores, \( \beta = 0.28, p < 0.012 \), with a slight decrement in scores in the heavier group that was within average range (Singer et al., 2012b). This was the only time point at which mental outcomes were affected, possibly because many items on the test at 12 months have a significant motor component.

When MDI and PDI scores were analyzed through mixed model longitudinal analyses using measures from all time points (4, 12, 18, and 24 months), no significant effects were found for MDI. However, there was a significant main effect of MDMA exposure on motor outcomes, with the heavier MDMA-exposed group showing motor delays compared with lighter and nonexposed children, PDI = 90.8 (SE = 3.8) for heavier versus 98.7 (SE = 1.4) for lighter and nonexposed at 24 months.

**DISCUSSION**

This series of studies was undertaken to investigate whether use of recreational MDMA during pregnancy was damaging to the children of ecstasy-using mothers. The main findings were that prenatal exposure to MDMA led to an alteration in sex ratio, significantly lower cognitive development scores (MDI) at 12 months of age, and persistent and significantly poorer motor quality and milestone achievement over the first 2 years of life, controlling for polysubstance exposure and other confounding variables. At 12 months of age, higher amounts of prenatal exposure had negative effects on both cognitive and motor outcomes and motor quality, controlling for multiple confounding factors. Motor deficits were identifiable at 4 months and persisted through 24 months of age on standardized, normative outcome measures, while mental outcomes were only different at 12 months.

Because so few women continued to use MDMA after the first trimester, findings could be attributed only to first trimester exposure.

There may be persistent mediated effects of MDMA via the release of stress hormones in the pregnancy period. Stress hormones, in particular cortisol, may have neurotoxic effects on hypothalamic–pituitary–adrenal axis development in infancy, and levels of these hormones appear to be increased when MDMA use has been high (Parrott, 2009). In the case of pregnant women, higher levels could persist for some time after the last use of the drug (Parrott, 2014). In MDMA-using dance clubbers, cortisol levels are increased by around 800%, thought to be influenced by thermal stress, physical exertion, and psychosocial stimulation (Parrott, 2009).
Likewise, MDMA is known to pass through the placental barrier to the fetus (Campbell et al., 2006). Serotonin, the neurotransmitter primarily affected by MDMA use, has significant effects on the development of the fetal brain, and the serotonin system is involved in various components of motor control (Jacobs and Fornal, 1995). Alterations in the serotonin system during fetal development are associated with changes in somatosensory systems and motor output (Wurtman, 2005).

Findings of alterations in sex ratio are of interest as several epidemiologic studies implicate the influence of fetal toxins on sex ratios, for example, with dioxin (Mocarelli et al., 2000) and polybrominated biphenyl exposure (Terrell et al., 2009), although mechanisms are unknown.

The present study has both strengths and limitations. Strengths include a prospective longitudinal design, control for polysubstance exposure, and other confounding variables, which are known to impact child outcomes, such as the home environment. Limitations include the small sample size, the absence of biomarkers of substance exposure, and the self-selection of a voluntary group, which could introduce selection bias. However, the homogeneous sample, of middle socioeconomic status, did not have many of the risk factors found in other studies of drug exposure.

CONCLUSIONS

There is extensive empirical evidence on the adverse effects of recreational stimulants, because when taken regularly, they impair the psychobiological integrity of adolescents and adults (Feyissa and Kelly, 2008; Cruickshank and Dyer, 2009; Schifano et al., 2011; Carvalho M et al., 2012.; Panenka et al., 2013; Parrott, 2013b; Parrott, 2013a). Many young female drug users may be at risk of becoming pregnant, and hence, it is particularly important to investigate the effects of drug usage within this subgroup. The adverse effects of cocaine on the developing fetus are well established. (Singer et al., 2008).

Because the early fine and gross motor delays found in children of MDMA users in this study may indicate risk for later learning problems, long-term follow-up is needed to assess whether deficits persist and affect school-age functioning. Given the widespread but erroneous view that MDMA is a safe drug and because of its pervasive recreational use among women of child-bearing age, pregnant women should be cautioned about potential adverse developmental effects—as revealed in this study. Note that women also need to be made aware that negative outcomes may be found even when women stop using MDMA prior to pregnancy. There is also the urgent need to study other more recent recreational drugs (so called Novel Psychoactive Substances or “legal highs”) such as mephedrone (Schifano et al., 2011), when taken during human pregnancy and to have a better understanding of the interactions between multiple drug use and exposure to other known risks, including maternal stress.

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