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

Lynn T. Singer[1],[*], **Derek G. Moore**[2], **Meeyoung O. Min**[1], **Julia Goodwin**[2], **John J. D. Turner**[2], **Sarah Fulton**[1], and **Andrew C. Parrott**[3]

[1]Case Western Reserve University, Cleveland, Ohio, USA

[2]The University of East London, London, UK

[3]Swansea 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.

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 child-bearing 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 hypertonic (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 BRS 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.

Acknowledgments

References

Bayley, N. Bayley Scales of Infant Development: Manual. Psychological Corp; New York, NY: 1993.

Campbell NG, Koprich JB, Kanaan NM, Lipton JW. MDMA administration to pregnant Sprague–Dawley rats results in its passage to the fetal compartment. Neurotoxicol Teratol. 2006; 28(4):459–465. [PubMed: 16905291]

Carvalho M, Carmo H, Costa VM, et al. Toxicity of amphetamines: an update. Arch Toxicol. 2012; 86(8):1167–1231. [PubMed: 22392347]

Cruickshank CC, Dyer KR. A review of the clinical pharmacology of methamphetamine. ADD Addict. 2009; 104(7):1085–1099.

Degenhardt L, Bruno R, Topp L. Is ecstasy a drug of dependence? Drug Alcohol Depend. 2010; 107(1):1–10. [PubMed: 19836170]

Derogatis, LR. The Brief Symptom Inventory (BSI): Administration, Scoring & Procedures Manual—II. Clinical Psychometric Research; Towson, MD: 1992.

Feyissa AM, Kelly JP. A review of the neuropharmacological properties of khat. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(5):1147–1166. [PubMed: 18561890]

Green AR, Mechan AO, Elliott JM, O'shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Pharmacol Rev. 2003; 55(3):463–508. [PubMed: 12869661]

Jacobs, BL.; Fornal, CA. Serotonin and behaviour: a general hypothesis. In: Bloom Fe, KD., editor. Psychopharmacology. Raven Press Ltd; New York: 1995. p. 461-469.

Kish SJ, Lerch J, Furukawa Y, et al. Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[(11)C]DASB and structural brain imaging study. Brain. 2010; 133(Pt 6):1779–1797. [PubMed: 20483717]

Lester BM, Tronick EZ. History and description of the Neonatal Intensive Care Unit Network Neurobehavioral Scale. Pediatrics. 2004; 113(3 Pt 2):634–640. [PubMed: 14993523]

McCann UD, Szabo Z, Vranesic M, et al. Positron emission tomographic studies of brain dopamine and serotonin transporters in abstinent (+/−) 3,4-methylenedioxymethamphetamine ("ecstasy") users: relationship to cognitive performance. Psychopharmacology. 2008; 200(3):439–450. [PubMed: 18661256]

McElhatton PR, Bateman DN, Evans C, Pughe KR, Thomas SH. Congenital anomalies after prenatal ecstasy exposure. Lancet. 1999; 354(9188):1441–1442. [PubMed: 10543673]

Mocarelli P, Gerthoux PM, Ferrari E, et al. Paternal concentrations of dioxin and sex ratio of offspring. Lancet. 2000; 355(9218):1858–1863. [PubMed: 10866441]

Moore DG, Turner JD, Parrott AC, et al. During pregnancy, recreational drug-using women stop taking ecstasy (3,4-methylenedioxy-N-methylamphetamine) and reduce alcohol consumption, but continue to smoke tobacco and cannabis: initial findings from the Development and Infancy Study. J Psychopharmacol. 2010; 24(9):1403–1410. [PubMed: 19939863]

Moore DG, Turner JJD, Goodwin JE, Fulton SE, Singer LT, Parrott AC. In utero exposure to the popular 'recreational' drugs MDMA (ecstasy) and methamphetamine (ice, crystal): preliminary findings. Clin Dev Med. 2011; 188:169–182.

Panenka WJ, Procyshyn RM, Lecomte T, et al. Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. Drug Alcohol Depend. 2013; 129(3):167–179. [PubMed: 23273775]

Parrott AC. Why all stimulant drugs are damaging to recreational users: an empirical overview and psychobiological explanation. Hum Psychopharmacol. 2014 Submitted. Under Review.

Parrott AC. Cortisol and 3,4-methylenedioxymethamphetamine: neurohormonal aspects of bioenergetic stress in ecstasy users. Neuropsychobiology. 2009; 60(3–4):148–158. [PubMed: 19893332]

Parrott AC. Human psychobiology of MDMA or 'ecstasy': an overview of 25 years of empirical research. Hum Psychopharmacol. 2013a; 28(4):289–307. [PubMed: 23881877]

Parrott AC. MDMA, serotonergic neurotoxicity, and the diverse functional deficits of recreational 'ecstasy' users. Neurosci Biobehav Rev. 2013b; 37(8):1466–1484. [PubMed: 23660456]

Parrott AC, Moore DG, Turner JJ, Goodwin J, Min MO, Singer LT. MDMA and heightened cortisol: a neurohormonal perspective on the pregnancy outcomes of mothers used 'ecstasy' during pregnancy. Hum Psychopharmacol. 2014; 29(1):1–7. [PubMed: 24424703]

Piper BJ. A developmental comparison of the neurobehavioral effects of ecstasy (MDMA). Neurotoxicol Teratol. 2007; 29(2):288–300. [PubMed: 17174068]

Piper MC, Pinnell LE, Darrah J, Maguire T. Construction and validation of the Alberta Infant Motor Scale (AIMS). Can J Public Health. 1992; 83:546–550.

Powell CM, Michaelis RC. Townes–Brocks syndrome. J Med Genet. 1999; 36(9902):89–93. [PubMed: 10051003]

Riley, EP.; Vorhees, CV. Handbook of Behavioral Teratology. Plenum Press; New York: 1986.

Schifano F, Albanese A, Fergus S, et al. Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. Psychopharmacology. 2011; 214(3):593–602. [PubMed: 21072502]

Singer LT, Nelson S, Short E, et al. Prenatal cocaine exposure: drug and environmental effects at 9 years. J Pediatr. 2008; 153(1):105–111. [PubMed: 18571546]

Singer LT, Arendt R, Minnes S, et al. Cognitive and motor outcomes of cocaine-exposed infants. JAMA. 2002; 287(15):1952–1960. [PubMed: 11960537]

Singer LT, Linares TJ, Ntiri S, Henry R, Minnes S. Psychosocial profiles of older adolescent MDMA users. Drug Alcohol Depend. 2004; 74(3):245–252. [PubMed: 15194202]

Singer LT, Moore DG, Fulton S, et al. Neurobehavioral outcomes of infants exposed to MDMA (ecstasy) and other recreational drugs during pregnancy. Neurotoxicol Teratol. 2012a; 34(3):303–310. [PubMed: 22387807]

Singer LT, Moore DG, Min MO, et al. One-year outcomes of prenatal exposure to MDMA and other recreational drugs. Pediatrics. 2012b; 130(3):407–413. [PubMed: 22908109]

Skelton MR, Williams MT, Vorhees CV. Developmental effects of 3,4-methylenedioxymethamphetamine: a review. Behav Pharmacol. 2008; 19:91–111. [PubMed: 18332674]

Skinner, HA. Drug Use Questionnaire (DAST-20). Addiction Research Foundation of Ontario; Toronto, Canada: 1982.

Terrell ML, Berzen AK, Small CM, Cameron LL, Wirth JJ, Marcus M. A cohort study of the association between secondary sex ratio and parental exposure to polybrominated biphenyl (PBB) and polychlorinated biphenyl (PCB). Environ Health. 2009; 8:35.doi: 10.1186/1476-069x-8-35 [PubMed: 19682390]

Turner JJ, Parrott AC, Goodwin J, et al. Psychiatric profiles of mothers who take ecstasy/MDMA during pregnancy: reduced depression 1 year after giving birth and quitting ecstasy. J Psychopharmacol. 2014; 28(1):55–61. [PubMed: 24327452]

Wechsler, D. Wechsler Abbreviated Scale of Intelligence: WASI. Psychological Corp., Harcourt Brace; San Antonio, TX: 1999.

Wurtman RJ. Genes, stress, and depression. Metab Clin Exp. 2005; 54(5 Suppl 1):16–19. [PubMed: 15877307]

Zimmerman, IL.; Steiner, VG.; Pond, RE., editors. PLS-3: Preschool Language Scale—3. The Psychological Corporation; San Antonio, TX: 1992.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript