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Neurobehavioral outcomes of infants exposed to MDMA (Ecstasy) and other recreational drugs during pregnancy☆

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ABSTRACT

3,4-methylenedioxymethamphetamine (MDMA) or "Ecstasy" is one of the most widely used illicit recreational drugs among young adults. MDMA is an indirect monoaminergic agonist and reuptake inhibitor that primarily affects the serotonin system. Preclinical studies in animals have found prenatal exposure related to neonatal tremors and long-term learning and memory impairments. To date, there are no prospective studies of the sequelae of prenatal exposure to MDMA in humans, despite concerns about its potential for harmful effects to the fetus. The present study is the first to prospectively identify MDMA-using women during pregnancy and to document patterns and correlates of use with neonatal and early infancy outcomes of offspring.

All mothers and infants were prospectively recruited through the Case Western Reserve University (CWRU) and University of East London (UEL) Drugs and Infancy Study (DAISY) that focused on recreational drug use in pregnant women. Women were interviewed about substance use prior to and during pregnancy and infants were seen at 1 and 4 months using standardized, normative assessments of neonatal behavior, and cognitive and motor development, including the NICU Network Neurobehavioral Scale (NNNS), the Bayley Mental and Motor Development Scales (MDI, PDI), and the Alberta Infant Motor Scales (AIMS). The sample was primarily middle class with some university education and in stable partner relationships. The majority of women recruited had taken a number of illicit drugs prior to or during pregnancy. Group differences between those polydrug using women who had specifically used MDMA during pregnancy (n = 28) and those who had not (n = 68) were assessed using chi-square and t-tests. MDMA and other drug effects were assessed through multiple regression analyses controlling for confounding variables.

Women who used MDMA during pregnancy had fewer prior births and more negative sequelae associated with their drug use, including more health, work, and social problems. MDMA exposed infants differed in sex ratio (more male births) and had poorer motor quality and lower milestone attainment at 4 months, with a dose–response relationship to amount of MDMA exposure. These findings suggest risk to the developing infant related to MDMA exposure and warrant continued follow-up to determine whether early motor delays persist or resolve.

1. Introduction

3,4-methylenedioxymethamphetamine (MDMA) or "Ecstasy" is one of the most widely used illicit recreational drugs among young adults, often associated with the club dance culture known as "raves" in Europe, Australia, and the United States. In the United Kingdom, it has been estimated that about a half million tablets of MDMA are taken each weekend, often in conjunction with other drugs (Parrott et al., 2008). Significant use in the U.S. is documented through the Monitoring the Future Study indicating use levels as high as 9.5% for 12th graders and college students, both at "raves" and in private social settings (Johnston et al., 2005; Singer et al., 2004). In the National Survey on Drug Use and Health Data from 1999 to 2008, MDMA was more likely to be used by young women than young men over the ten year period (Wu et al., 2010) raising concerns about reproductive risk and fetal outcomes.

To date, there are no prospective studies of the sequelae of prenatal exposure to MDMA, despite concerns about its potential for harmful effects to the fetus. MDMA is a powerful monoaminergic agonist that

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both inhibits the reuptake and promotes the release of serotonin (5-HT) and dopamine, with both stimulant and hallucinogenic effects (Rudnick and Wall, 1992). The psychobiological consequences of taking MDMA can be very significant for adults, and may induce a range of maternal effects with known negative consequences for the fetus. In acute terms, MDMA causes psychophysiological overstimulation and hyperthermia (Freedman et al., 2005), and an increase in the stress neurohormone cortisol (Parrott et al., 2008). In the days following recreational use of Ecstasy/MDMA, there are adverse neuropsychobiological changes in users, with increased feelings of sadness, anger and behavioral aggression, impaired sleep, decreased appetite, and lowered food intake (Hoshi et al., 2006; Parrott, 2006; Singer et al., 2004; Turner et al., 1998). The long-term cumulative effects of regular use include serotonergic changes, cognitive impairments, memory deficits, impaired judgment, reduced social intelligence, sleep disturbance, and heightened psychological distress (Fisk et al., 2005; Harris et al., 2002; Kish et al., 2010; McCann and Ricaurte, 2007; McCann et al., 2009; Milani et al., 2005; Parrott, 2006, 2009; Reay et al., 2006).

The preclinical literature indicates that prenatal MDMA exposure may have adverse effects on developing brain and behavior and has recently been reviewed (Piper, 2007; Skelton et al., 2008).

In an early study of day old chicks (Bronson et al., 1994), exposure to MDMA prenatally produced significant behavioral effects, including tremors, wing extension, reflex abnormalities, and convulsive kicking. Although the mechanisms by which MDMA might affect development are unknown, studies have demonstrated effects on the serotonin system, with significant reductions in neonatal levels of serotonin in the hippocampus in rat pups (Meyer et al., 2004; Schaefer et al., 2008) persistent to adulthood (Crawford et al., 2006).

Animals prenatally exposed also show reduced levels of dopamine metabolites in several brain areas which are implicated in fetal brain organization and learning (Koprich et al., 2003).

Vorhees et al. (2004) reported the first evidence that exposure to MDMA in rats during stages analogous to early and late third trimester human fetal brain development induces specific types of long-term learning and memory impairments. Consistent with the findings of reductions in serotonin metabolites in the hippocampus, Vorhees (Vorhees et al., 2004; Vorhees et al., 2009; Vorhees et al., 2007; Williams et al., 2003) found MDMA related deficits specific to spatial learning. Work by Koprich et al. (2003) indicates that prenatal exposure equivalent to the first trimester also produced significant neurochemical and behavioral alterations in neonatal rat pups. Prenatally exposed MDMA animals had increased locomotor activity and lack of habituation in a novel cage environment.

To date there have been no human studies of developmental outcomes of prenatal MDMA exposure, but tracking of 136 pregnancies in which MDMA was used through the UK National Teratology Information Services indicated a 4–7 times higher risk for congenital malformations, particularly cardiovascular and musculoskeletal anomalies with MDMA exposure (McElhatton et al., 1999). Even after accounting for the higher prevalence of malformations in higher risk pregnancies, MDMA exposure was associated with a two-fold risk. The present study is the first to prospectively identify MDMA-using women during pregnancy and to document patterns and correlates of use with neonatal and early infancy outcomes of offspring.

2. Methods

2.1. General method

2.1.1. Participants

All mothers and infants were prospectively recruited through the Case Western Reserve University (CWRU) and University of East London (UEL) Drugs and Infancy Study (DAISY) that focused on recreational drug use in pregnant women (Moore et al., 2011; Moore et al., 2010). Participants were recruited through either referral by midwives, response to leaflets describing the study distributed at prenatal clinics, or advertisements in pregnancy magazines. Study description requested participation of pregnant women who had used recreational drugs during pregnancy and listed Ecstasy, tobacco, cannabis, alcohol, and cocaine as examples. Thus the majority of women were "polydrug" users. Exclusionary factors for both groups include maternal/child HIV positive status, maternal moderate/severe mental retardation or severe psychiatric or medical illness; or, for the child, other major medical illnesses. All participants were informed that their data would remain confidential and gave informed written consent under protocols approved by university (CWRU and UEL) and National Health Service (UK) ethics committees.

Of 126 women who responded to advertisements, five did not meet study criteria, and 25 who requested and were sent materials did not come to the first visit (4 had miscarriages, 1 withdrew due to depression, 2 withdrew due to partner's objection, 1 moved out of testing range and withdrew, 3 withdrew with no reason given, and 14 could not be contacted). Thus, 96 subjects were enrolled and seen for infant testing during the course of the study. Of these, 82 infants were seen at one month and 87 at four months.

2.1.2. Measures of MDMA exposure and covariates

All women were interviewed regarding their substance use by trained research assistants either in their homes, at the UEL laboratory, or, for a small number, by telephone. Attempts were made to interview women over the course of the pregnancy on 3 separate occasions, but if necessary, a combined set of interviews was given on one occasion if enrollment was late in the pregnancy (Moore et al., 2010). Sixty two women completed the interview during pregnancy, while 24 were interviewed postnatally.

2.1.2.1. Prenatal levels of drug exposure. The interview was an adaptation of the Maternal Post-Partum Interview used in prior studies of alcohol and cocaine exposure (Singer et al., 2002) and asked women to describe their intake of substances commonly used in UK cohorts based on prior UEL drug questionnaires (Parrott et al., 2001). Part 1 requested information about total lifetime drug use and use during the year leading up to conception. Part 2 asked about drug use in the month prior to pregnancy and over the first 2 trimesters, and Part 3 asked about use in the last trimester. For each section, values were computed for tobacco/cigarettes (#), alcohol (# units), marijuana joints/cigarettes (#), MDMA tablets (#), heroin, cigarettes or injections (#), ketamine (grams), crack (# rocks) or cocaine (# lines), benzodiazepine and LSD tablets (#), and hallucinogenic mushrooms (#). In the United Kingdom a standard unit of alcohol is defined as 10 ml, in contrast to the United States measure of 18 ml. Frequency of use for each drug was recorded on a scale ranging from 0 (none) to 7 (daily use). An average dose per week for each drug was calculated by multiplying the frequency by the amount taken per occasion. All women were classified as users if they self-admitted on clinical interview to MDMA use during pregnancy or in the month prior to pregnancy. Women who had used prior to this time point but reported no use during pregnancy ($n = 32$) or who had never used were classified as non-users, since we were interested in the outcome of fetal exposure.

The initial interview also obtained information for each drug on age at first use, age when drug use was discontinued, and typical and highest consumption. In addition, participants were asked whether friends had suggested reduced intake and whether they had experienced occupational, health, relationship, psychological, or legal difficulties related to drug intake. Participants were asked to estimate the number of occasions they had taken MDMA over their lifetime, their physical sensations when taking MDMA, and whether they had used MDMA while dancing/clubbing.

2.1.2.2. Maternal drug severity demographics and psychological measures. Women were also administered the Drug Abuse Screening Test (DAST)

(Skinner, 1982) as close as possible to their first interview to characterize the level of their drug dependence. The DAST is a 20 item self-report scale validated against the DSM-III that yields a quantitative index of the degree of problems related to drug use, with a cutoff score of 16 (out of 20) indicating a severe level of secondary problems in life areas of marital and social relations, and employment, legal, physical, and medical problems.

The Brief Symptom Inventory (BSI) (Derogatis, 1992), a widely used self-report, 53 item questionnaire was also given to describe experience of a range of psychiatric symptom patterns. The BSI yields 9 subscales (somatic complaints, obsessive compulsive behavior, interpersonal sensitivity, depression, anxiety, phobic anxiety, paranoid ideation, hostility and psychoticism) that possess consensually valid clinical significance. A summary score, the General Severity Index (GSI), measures overall psychological distress. Cut off scores identify subjects whose symptoms reach severity levels suggestive of the need for clinical intervention, i.e. >the 84th percentile (moderate) or >the 98th percentile (severe) compared to same sex, non-patient norms. For this analysis, BSI data from the one month visit were used.

Data on maternal age at infant birth, marital status, ethnicity, educational level, and household income were obtained. Women were also administered two subsets of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), a standardized IQ test, i.e. the Block Design, and the Similarities Scales. Each scale yields a t score with a mean of 50 and a standard deviation of 8.

2.1.2.3. Infant birth and behavioral measures. After infant birth, fetal growth measurements (weight, length, head circumference, and gestational age) and health information were taken from hospital records. Sample sizes are smaller for some parameters due to limited access to hospital records.

Infants were seen for follow-up at the UEL laboratories designed for the study. All infants were administered the NICU Network Neurobehavioral Scale (NNNS) (Lester and Tronick, 2004) at approximately 1 month corrected age by the same examiner masked to infant drug status and trained and certified in the procedure by gold standard reviewers. The NNNS assesses three aspects namely neurologic, behavioral, and stress/abstinence functioning in drug exposed or high risk infants. The neurologic component includes assessment of tone and primitive reflexes. The behavioral scale assesses items thought to be sensitive to drug effects, including habituation, attention, arousal, regulation, movement quality, excitability, and lethargy. Both components are scored on Likert-type scales ranging from 1–3 to 1–9 points. Forty nine stress/abstinence behaviors are scored as present (1) or absent (0). The items have been reduced to 13 summary scores, for which coefficient alpha statistics range from .56 to .82 for mean scores. The scale was administered in a quiet room with the infant initially asleep. However, habituation was not analyzed as too few infants were asleep at the beginning of the exam, as required for the item.

The Alberta Infant Motor Scale (AIMS) (Piper, 1992), an observational assessment scale constructed to measure gross motor maturation and milestone attainment in infants from birth through independent walking, was given at child age 4 months corrected for gestational age at birth. The AIMS contains 58 items divided into 4 subscales (prone, supine, sit, and stand). It has been normed on 2202 infants aged 1 week to 18 months. Raw scores can be converted to centile ranks for comparison to age-equivalent peers in the normative sample. The AIMS has excellent inter-rater and test-rater reliability and validity. At 4 months, scores at the tenth percentile or less are considered at risk (Darrah et al., 1998).

The Bayley Scales of Infant Development (Bayley, 1993) are widely used standardized assessments of infant development. The Mental Scale yields a Mental Development Index (MDI), a standard score reflecting memory, language, and problem solving abilities. The Psychomotor Index (PDI) measures gross and fine motor control and coordination. Normative data from the scales yield a mean of 100 and standard deviation of 15. The Behavioral Rating Scale (BRS) assesses quality of infant performance across several developmental domains based on the assessor's observations. At 4 months, the scale assesses two domains: Attention/Arousal and Motor Quality. Motor quality considers the overall quality of muscle tone and fine and gross motor movements. Percentile scores are derived from the total raw and factor scores. BRS scores can be categorized as within normal limits, questionable, and non-optimal. All assessors were master's level psychology assistants or the equivalent and were masked to infant drug exposure.

2.1.3. Statistical analyses

The primary group comparison was between polydrug or non-drug using mothers who took MDMA during pregnancy (n = 28) and polydrug using mothers who had not (n = 68). In regression analyses, MDMA use was defined dichotomously (coded as 1 for use), or as the number of tablets of MDMA used averaged over each trimester and the month prior to pregnancy.

Group differences between these two groups were examined using chi-square or Fisher's exact test for dichotomous variables and t- test or Wilcoxon Mann Whitney test. Log transformations were used where necessary to correct skewness. Univariate analyses were conducted on maternal factors and prenatal drug use. Spearman correlation analyses were used to assess relationships of amount and frequency of drug exposure to infant outcomes to determine covariates. Multiple linear regression analyses were performed to determine the significant predictors of the outcome measures controlling for covariates that were correlated with the outcome ($p<.20$) and MDMA status ($p<.20$).

Covariates considered included infant age at testing, all maternal demographic and infant birth variables, maternal use of other drugs during pregnancy, and maternal psychological distress. With alpha = .05 and power of .80, the sample size could detect moderate effect sizes with up to four predictors in regression models.

In order to determine the effect of prenatal and lifetime MDMA exposure on NNNS, various multivariate analyses were performed depending on the distributional property of the outcome variables. Ordinary least squares (OLS) analyses were performed on normally distributed continuous outcome variables such as attention, arousal, regulation, quality of movement, handling, and stress abstinence; Poisson regression on lethargy and asymmetrical reflexes; negative binomial regression on excitability and non-optimal reflexes; and logistic regression on hypertonicity and hypotonicity.

If there were significant effects from univariate analyses on child outcomes, covariates related to both outcome and MDMA status were then added for consideration in analyses. Other drug use and sociodemographic covariates that were different by group and related to the outcome at $p<.2$ were evaluated in the regression model stepwise and retained if, on entry, they were significant at $p<.10$ or caused substantial change (>10%) in the MDMA coefficient. Each regression was also run with average lifetime use of MDMA to explore possible residual effects of heavy lifetime use. Lifetime use was defined as the total number of tablets consumed over the lifetime. We further divided MDMA users into heavier (n = 13) and lighter (n = 15) users based on a median split.

For three group analyses, Analyses of Variance (ANOVA) was used. When there was an overall effect ($p<.10$), planned post-hoc analyses were conducted comparing heavier to lighter and non-exposed infants.

3. Results

3.1. Maternal outcomes

Table 1 reports demographic, medical, and psychological characteristics of women who used MDMA vs. women who did not use MDMA while pregnant. The maternal sample was primarily white; married or with a partner; with some university education; came from a full range of socioeconomic (SES) classes, with many from

Table 1
Maternal demographics, IQ, drug, and psychological status.

	Non-MDMA (n = 68) n (%)	MDMA exposed (n = 28) n (%)	χ^2/t	p
White	57 (84)	23 (85)	0.3	0.87
Registered disabled (mother)	5 (8)	0 (0)	0.19	0.32
Married/with partner	57 (84)	22 (79)	0.38	0.54
Family income			1.59	0.81
<10K British pounds	13 (19)	4 (14)		
10–2K British pounds	16 (24)	6 (21)		
20–30K British Pounds	13 (19)	8 (29)		
30–40K British pounds	11 (16)	3 (11)		
>40 K British pounds	15 (22)	7 (25)		
	M (SD)	M (SD)		
Maternal age at birth	30.3 (6.4)	28.4 (6.2)	1.33	0.19
Maternal education[a]	14.9 (2.9)	15.3 (2.7)	−0.57	0.57
WASI[b] block design	56.0 (9.5)	57.0 (8.1)	−0.43	0.67
WASI[b] similarities	49.4 (8.9)	51.4 (8.5)	−0.88	0.38
Parity	1.88 (1.11)	1.21 (0.42)	4.27	.0001
General Severity Index (GSI)	0.51 (0.47)	0.71 (0.81)	−0.61	0.54
GSI 84th%tile, n (%)	13 (23.6)	7 (31.8)	0.55	0.46
GSI 98th%tile, n (%)	6 (9.1)	4 (18.2)	1.26	0.27
DAST[c] score	4.6 (4.4)	7.7 (4.1)	−3.09	0.03
DAST[c] score > 16, n (%)	2 (2.9)	1 (3.6)	.026	.99

[a] The compulsory point of entering school in the UK is at ages 4–5 (reception level) and the age of leaving (with general certificates of secondary education, GCSEs) is at age 16 (11 years of education). However many continue into "sixth-form college" and do advanced level qualifications (A'Levels) and leave at age 18 (13 years of education). University "undergraduate" attendance then typically continues from age 19 to 22 (14–16 years of education).
[b] Wechsler Abbreviated Scale of Intelligence.
[c] Drug Abuse Screening Test (DAST Score).

middle and high SES backgrounds; and was overall in the average range of intellectual ability. MDMA using women differed from non-using women only in having fewer children. Overall prenatal drug use and the negative sequelae of drug use as measured by the DAST were significantly different between the groups (Tables 1, 2, and 3). Women who used MDMA during pregnancy had higher scores on the DAST, indicating greater severity of sequelae related to their drug use. However, the mean scores were below clinical significance for both groups, with <5% for each group scoring above the cutoff.

Table 2 describes the group average and median drug use for the MDMA and non-MMDA users across the full range of substances reported. Table 3 describes the percentage of women in each group that used a particular drug and the average amount of use across pregnancy and the month prior only for the subset who reported using the drug. MDMA users were more likely to have used ketamine, cocaine, amphetamines, LSD, tranquilizers, and opiates during their lifetime, and were more likely to use tobacco, marijuana, cocaine, amphetamines, LSD, and mushrooms during their pregnancy.

Table 4 shows the average amount of MDMA, alcohol, tobacco, and cocaine taken during the month prior to and during the trimesters of pregnancy. Though groups did not differ in the percentage that used tobacco or marijuana prior to pregnancy, non-MDMA users were more likely to decrease their use of these drugs during pregnancy than MDMA users. Over the pregnancy, most MDMA users discontinued use, with only one woman reporting to use in the third trimester.

MDMA users who were prior users and continued to use during pregnancy reported having first used the drug at a mean age of 20.2 years (S.D. = 4.4, R = 14–29). They had used MDMA on average of 171 times over their lifetime, (S.D. = 195, R = 6–936), typically ingesting an average of 3 tablets on days they used the drug (S.D. = 2, R = 1–8). The most MDMA taken on any one occasion averaged 7.4 tablets (S.D. = 5.3, R = 2–20).

Prior to pregnancy, the mean number of tablets ingested per week was 3.2 (S.D. = 5.2, Range 0.1–26.3) for those who used MDMA during pregnancy. The mean total amount of MDMA used during pregnancy and the month prior was 25 tablets (S.D. = 43.7, Range 0.45–180). Most (61%) MDMA users took the drug while attending dances or clubs and experienced moderate to strong feelings of being hot/sweaty. On interview, 30% of the MDMA users reported that friends or relatives had suggested that they reduce Ecstasy intake and 77% identified at least one occupational, health, relationship, or legal difficulty related to intake. In the non-MDMA group, several women also reported having used MDMA prior to pregnancy, with a mean lifetime use per week of .70 (S.D. = 1.54, Range 0–7.5).

Because drugs may have effects only at certain thresholds, MDMA users were divided into heavier (n = 13) and lighter (n = 15) groups based on a median split for the amount taken averaged over the pregnancy (median = 0.14). Heavier users averaged 3.3 (±4) tablets in the month prior to pregnancy compared to .12 ± .2 tablets for lighter users (Wilcoxin test $p < .007$); 1.6 ± 2 vs. .12 ± 1 tablets in the first trimester ($p < .12$), and .15 ± .6 vs. .02 ± .1 in the second trimester, $p > .20$. Only one mother reported using MDMA in the third trimester.

Lighter and heavier users did not differ in the number of tablets they reported taking over their lifetime of use (Means = 173.9 ± 243 vs. 169.1 ± 142 for lighter vs. heavier, $z = .59$, $p < .55$), but were marginally different in the year prior to pregnancy (8.9 ± 12 vs. 28.4 ± 26, $z = 1.7$, $p < .09$), with heavier users reporting three times the amount of use of lighter users, on average.

3.2. Birth and neonatal child outcomes

All births were singleton births. Child birth outcomes (Table 5) did not differ by group in gestation period, birthweight, prematurity, length, or head circumference although this finding is inconclusive for birth length and head circumference due to missing data. However, MDMA-exposed infants were significantly more likely to be male (71% vs. 46%). This remained the case even after controlling for other drug

Table 2
Average maternal drug use during pregnancy by group.

Drug (per week)	Non-MDMA		MDMA		Z[a]	p
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)		
Cigarettes	32.5 (49.1)	13.19 (0–280)	36.0 (39.9)	16.3 (0–123)	1.30	0.19
Alcohol (units)	6.6 (12.9)	2.3 (0–84)	9.1 (11.6)	5.2 (0–51)	2.06	0.04
Marijuana (joints)	6.3 (15.0)	0.06 (0–88)	9.7 (19.3)	1.4 (0–88)	1.96	0.05
MDMA (tablets)	–	–	0.6 (1.1)	0.13 (.01–4.5)	–	–
Cocaine (doses)	0.2 (0.1)	0 (0–.8)	0.2 (0.5)	0.02 (0–2.4)	4.91	.0001
Crack (rocks)	1.0 (5.0)	0 (0–38)	0.02 (0.1)	0 (0–.4)	0.62	0.54
Amphetamine (doses)	0.0003 (0.001)	0 (0–.01)	0.04 (0.1)	0 (0–.5)	2.16	0.03
Mushrooms (doses)	0 (0)	0(0–0)	1.89 (9.6)	0 (0–50)	2.76	.006
Tranquilizers (doses)	0.4 (1.9)	0 (0–11)	0.1 (0.6)	0 (0–3)	0.49	0.62
Opiates (doses)	0.2 (1.2)	0 (0–8)	0.1 (0.6)	0 (0–3.1)	0.28	0.78
LSD (doses)	0 (0)	0(0–0)	0.01 (0.1)	0 (0–.3)	2.71	.007
Ketamine	0	0	0.009 −(0.004)	0 (0–0.02)	2.20	0.03

[a] Wilcoxon Mann Whitney test.

Table 3
Incidence and average drug use during pregnancy among those who used the drug[a].

	Non-MDMA (n = 68)			MDMA (n = 28)			χ^2	Z
	n %	Mean	SD	n %	Mean	SD		
Cigarettes	42 (62)	53.05	53.5	24 (86)	42.05	40	5.29*	−0.98
Alcohol[b]	62 (91)	7.25	13.3	27 (96)	9.39	11.67	0.81	1.82
Marijuana	37 (54)	11.65	18.9	23 (82)	11.82	20.8	6.51*	−0.51
Cocaine	11 (16)	0.12	0.2	20 (71)	0.29	0.56	27.69	−0.27
Crack[b]	6 (9)	11.25	14.2	4 (14)	0.18	0.1	0.63	−2.24*
Amphetamine[b]	2 (3)	0.01	0	5 (18)	0.26	0.2	6.53*	−0.71
Mushrooms[b]	0	–	–	4 (14)	0.09	0.1	10.14**	–
Tranquilizers[b]	8 (12)	3.48	5	2 (7)	1.52	2	0.45	0
Opiates[b]	6 (9)	2.77	3.5	3 (11)	1.19	1.67	0.08	0
LSD	0	–	–	3 (11)	0.15	1	7.52	–
Ketamine	0	–	–	2 (7)	0.89	1.22	4.96	–

[a] chi square statistic was used for frequency and z statistic was used for the continuous variables.
[b] Fisher's Exact test.
* p<.05.
** p<.01.
*** p<.001.

differences with the O.R. of having a male birth after MDMA exposure = 3.2, (95% CI: 1.2–8.2, p<.02).

One child in the MDMA-exposed group was diagnosed with Townes–Brocks syndrome, a rare genetic autosomal dominant multiple malformation of the gene SALL1 (Powell and Michaelis, 1999)[1]. All outcome analyses with significant findings were rerun excluding this child and results did not differ. Thus, the presented findings include all in the MDMA-exposed group.

3.3. Neonatal behavioral outcomes

Table 6 presents results from the NICU Network Neurobehavioral Scale (NNNS). Infants were on average 33.6 days old (5.0 = 9.3; R = 17–59) when tested (MDMA group M = 34.0 ± 9.3 vs. 33.4 ± 9.3, t = .27, p = .78). There were no differences between groups when mean scores were compared. However, when score distributions were examined, there was a non-significant trend for MDMA-exposed infants to demonstrate more lethargic behaviors, (i.e., low levels of motor, state, and physiological reactivity) than non-MDMA exposed infants (91% vs. 73%, likelihood ratio $\chi^2 = 3.31$, p<.069). There was a similar trend for MDMA exposed infants to be less likely (9% vs. 27%, ratio $\chi^2 = 3.31$, p<.069) to manifest hypertonic responses in tone, but there were no differences in hypotonia.

3.4. Child outcomes at 4-months-old

At 4 months, there were no differences by group on the Bayley MDI or on the attention/arousal factor of the Behavioral Rating Scale. However, there were differences between groups on the BRS Motor Quality Scale, with MDMA-exposed infants demonstrating significantly poorer motor quality (see Table 7). After controlling for significant covariates (average alcohol exposure), MDMA use remained a significant predictor (β = −.21, t = 2.1, p<.05). MDMA-exposed infants were rated as less coordinated and more likely to have slower and delayed movements. There was a dose–response effect as well, with higher average MDMA use over pregnancy predicting poorer motor quality (β = −.24, t = −2.1, p<.042).

There were significant differences on the AIMS test (see Table 8) also at 4 months, with more heavily exposed MDMA infants performing less well than the non-MDMA or the lighter MDMA-exposed groups; and these effects remained after controlling for covariates. There was also a non-significant trend for heavily exposed MDMA infants to attain lower PDI scores than the other 2 groups.

Table 4
Average maternal drug use by trimester.

	Non-MDMA (n = 68)		MDMA (n = 28)		Z[a]
	M	SD	M	SD	
Cigarettes					
Month prior	53.42	61.58	61.74	70.68	0.94
1st trimester	28.16	48.11	44.78	49.51	2.29*
2nd trimester	25.43	50.38	19.78	29.84	0.68
3rd trimester	23.45	50.13	17.89	30.79	0.30
Alcohol					
Month prior	12.76	20.80	21.31	32.23	2.14*
1st trimester	6.95	16.90	12.07	16.63	2.31*
2nd trimester	3.37	10.70	1.49	1.94	−0.04
3rd trimester	3.12	10.66	1.33	1.81	−0.29
Marijuana					
Month prior	10.88	26.23	12.94	23.49	1.36
1st trimester	7.45	19.24	10.29	20.82	1.60
2nd trimester	3.76	9.85	8.74	19.10	0.96
3rd trimester	3.36	7.87	6.86	17.37	1.83^
Cocaine					
Month prior	0.04	0.19	0.51	1.15	4.48***
1st trimester	0.026	0.18	0.23	0.86	5.30***
2nd trimester	0.004	0.02	0.03	0.07	2.44*
3rd trimester	0.0009	0.006	0.011	0.049	1.03
MDMA					
Month prior	–	–	1.61	3.11	–
1st trimester	–	–	0.82	1.58	–
2nd trimester	–	–	0.08	0.38	–
3rd trimester	–	–	0.006	0.03	–

^p<.10.
[a] Wilcoxon Mann Whitney test.
* p<.05.
** p<.01.
*** p<.001.

[1] The child with Townes–Brocks syndrome in the present study was diagnosed at birth due to physical malformations. First identified in 1972, the malformation occurs in an estimated 1/250,000 births and affects fewer than 200 people worldwide with equal gender distribution. Several body parts are affected, with imperforate anus, and ear, hand, kidney, and genetic malformations the most common sequelae. Intellectual disability has been found in 10% of those identified. In 10% of cases, new gene mutations may occur in those with no family history of the disorder. Genetic testing of the infant and parents was undertaken indicating that the infant had the SALL1 mutation, and that neither parent was a carrier. For this participant, maternal drug history indicated that MDMA was the primary drug of exposure, with report of twice monthly ingestion of 8 tablets per episode in the first trimester, but no use reported in the last two trimesters. Cigarettes, alcohol, and some cocaine were also used. In the year prior to pregnancy, MDMA was taken 2–3 times monthly at about the same dose (8 tablets), with a maximum dose of 10 tablets. Cocaine, mushrooms, and ketamine were also used occasionally.

Table 5
Child demographics and birth outcomes.

	Non-MDMA (n = 68)	MDMA exposed (n = 28)	χ^2/t	p
White, n(%)	51 (75)	20 (71)	0.13	0.72
Male, n(%)	31 (46)	20 (71)	5.32	0.02
Special baby care unit, n(%)	8 (12)	3 (11)	0.27	1.00
Gestation (weeks), M(SD)	39.5 (1.5)	40.0 (1.6)	−1.41	0.16
Preterm (<37 weeks), n (%)[a]	1 (1.5)	1 (3.6)	0.43	0.50
Birth weight (g), M(SD)[b]	3344 (511)	3537 (500)	2.10	0.15
Birth length[c], M(SD)	51.4 (2.7)	52.0 (2.6)	−0.56	0.58
Head circumference (cm)[d], M(SD)	34.3 (1.9)	34.8 (1.8)	−0.97	0.34

[a] Fisher's exact test.
[b] Adjusted for infant gender.
[c] Based on reduced sample of 31 and 10.
[d] Based on reduced sample of 39 and 16.

3.5. Other drug effects

Several additional drugs were related to infant outcomes independent of MDMA effects. Higher alcohol exposure predicted poorer motor quality at four months ($\beta = -.36$, $p < .005$); higher marijuana exposure predicted poorer attention ($\beta = -.28$, $p < .02$) and poorer regulation ($\beta = -.27$, $p < .02$) on the NNNS at one month.

4. Discussion

On measures of neonatal neurobehavioral outcomes at 1 month and cognitive measures at 4 months postpartum there was little difference between MDMA exposed and non-MDMA exposed infants of polydrug using mothers of similar socioeconomic status and ethnicity in the UK. Overall, these scores for both the MDMA and non-MDMA infants were within normal ranges.

At 4 months, however, differences between groups were found on two measures of motor functioning, suggesting heightened developmental risk in the prenatally MDMA-exposed cohort. Some specific aspects of motor functioning differed, with MDMA-exposed infants at 4 months demonstrating lower quality of motor functioning, and more heavily exposed infants demonstrating less mature gross motor functioning than non- or lighter MDMA-exposed infants. Of interest, the four month motor functioning differences of slower and more delayed movements measured on the AIMS and Bayley scales were consistent with the one month trends of more lethargic behaviors found in the MDMA exposed group on the NNNS.

Very little research has been conducted on the psychomotor aspects of MDMA, despite the fact that the serotonin system is involved in various aspects of motor control. Adult MDMA users display repetitive grinding movements of the jaw due to the dense innervation of motor-neurons to the jaw, face, and neck (Jacobs and Fornal, 1995).

Table 6
NICU Network Neurobehavioral Scale (NNNS) scores, unadjusted.

	Non-MDMA (n = 60)	MDMA (n = 22)	Z[a]/t/χ^2	P
Attention	6.02 (1.0)	5.99 (1.2)	.36	.71
Arousal	3.98 (.7)	3.89 (.8)	−.55	.58
Regulation	5.90 (.7)	6.03 (.6)	.51	.60
Handling	0.27 (.2)	0.24 (.3)	−.48	.63
Quality of movement	5.29 (.6)	5.27 (.5)	−.76	.44
Excitability	2.35 (2.0)	1.64 (1.7)	−1.42	.15
Lethargy	2.63 (1.5)	3.14 (1.7)	1.23	.22
Non-optimal reflexes	4.00 (1.7)	4.00 (1.6)	.22	.82
Asymmetrical reflexes	1.23 (1.1)	1.45 (1.1)	.94	.34
Hypertonicity	0.33 (.7)	0.14 (.5)	−1.60	.11
Yes (>0), n (%)	16 (26.7)	2 (9.1)	2.9	.13
Hypotonicity (yes), n (%),	11 (18)	4 (18.4)	.00	.99
Stress abstinence	0.04 (.00)	0.04 (.00)	.18	.86

[a] Wilcoxon Mann Whitney test.

Table 7
Four-month outcomes by MDMA status, unadjusted.

	Non-MDMA (n = 65)	MDMA (n = 22)	t/χ^2	p
	M (SD)	M (SD)		
Bayley Scales of Infant Development				
Mental Development Index	98.6 (8.9)	99.1 (6.4)	−.25	.80
Psycho-Motor Development Index	94.3 (10.8)	96.50 (10.0)	−.84	.40
BRS attention/arousal factor	70.9 (23.9)	71.23 (23.8)	.05	.96
BRS motor quality factor	74.1 (23.8)	58.91 (20.7)	−2.61	.009
Alberta Infant Motor Scale				
Percentile rank	45.8 (27.7)	50.4 (27.9)	.66	.51
<10th percentile, n (%)	9 (14%)	3 (14%)	.003	.99

Many aspects of motor control also have a serotonergic input, although some studies (Jacobs and Fornal, 1995) note that serotonin is more implicated in movements employing gross skeletal muscle systems rather than those utilizing fine or discrete muscles. Additionally, findings from the preclinical literature indicate differences in motor quality in chicks prenatally exposed to MDMA (Bronson et al., 1994), and studies of offspring of rats exposed to MDMA showed variable (both higher and lower) locomotor activity relative to controls during a test period (Koprich et al., 2003), as well as hypoactivity after neonatal exposure (Cohen et al., 2005).

There are no other comparative human studies of MDMA exposure on motor development. Recent follow-up of methamphetamine-exposed children to 3 years found effects of fetal exposure on motor development after finding subtle negative effects at 1 year (Smith et al., 2011). Thus, early motor effects may be transient or signal long-term risk.

In addition to finding specific effects on motor development that can be predicted a priori from the preclinical animal literature, this study also found an unexpected difference in the secondary sex ratio of this cohort, with significantly more male births. We also found a rare genetic mutation in one participant. At this stage we cannot establish whether these effects are causally related to MDMA use, but we can speculate on the mechanisms that could be implicated.

Several recent epidemiologic studies suggest that toxins with known developmental risk may have an influence on sex ratios. For example, high levels of dioxin exposure from an industrial spill were related to a significant decline in male births in couples in which fathers were highly exposed (Mocarelli et al., 2000), supporting prior findings noted in studies of polychlorinated biphenyls (PCBs) and environmental pollutants (del Rio et al., 2002).Other studies have found increased odds of male birth, as in this study, with combined parental exposure to polybrominated biphenyls (PBB) (Terrell et al., 2009). PBB was used as a flame retardant in the 1970s in the United States and has since been discontinued due to its toxic effects. A similar bias for male births has been reported with maternal cannabis use (Tennes et al., 1985). The mechanisms by which alterations in sex ratio occur are not known, but speculative explanations include changes in parental hormonal levels during or around the time of conception (James, 1996), an increase in XY embryos, enhanced loss of XX embryos, or the survival of Y sperm over X sperm (Tildo et al., 2005). Kinsley and Svare (1988)

Table 8
Four-month outcomes by heavier, lighter, and non-exposed, unadjusted.

	Non-MDMA	MDMA		F/χ^2	p
		Lighter	Heavier		
Psychomotor Development Index, M (SD)	94.3 (11)	101.1 (10)	91.8 (8)	2.6	<.08
BRS motor quality factor	74.1 (23.8)	60.8 (21)	57.0 (21)	3.6	<.04
Alberta Infant Motor Scale					
Percentile, M (SD)	45.9 (28)	65.7 (23)	35.1 (24)	3.8	<.03
<10th percentile, n (%)	9 (14%)	0	3 (27%)	3.4	<.18

identified significantly higher (more male) sex ratios in litters produced by female mice stressed by restraint or heat and suggested that low gonadotropin or high testosterone levels were responsible.

MDMA has acute stimulatory effects on a range of neurohormones (Dumont and Verkes, 2006). In a recent study of Ecstasy using dance clubbers with drug presence confirmed in saliva samples, there was a significant peak increase of 800% in cortisol, together with a significant 75% increase in the male sex hormone testosterone in both males and females (Parrott et al., 2008). In laboratory studies, MDMA can significantly increase core body temperature (Freedman et al., 2005), while in dance clubbers even larger mean increases in skin temperature and core body temperature have been noted (Morefield et al., 2009). MDMA also delays ejaculation, so that sexual intercourse can be more prolonged and more thermally stressful. There may also be other physiological changes associated with the acute serotonin syndrome, such as thirst and dehydration, or excessive fluid intake and diluted sodium (Parrott, 2002). Currently it is not known if these physiological, neurohormonal and thermal factors differentially affect the survival of X sperm over Y sperm.

In the present study potential confounders such as maternal age and education and child birth order, race, and gestational age were not related to sex ratio, nor was other drug exposure. Maternal weight has also been implicated in changes in secondary sex ratio and may be relevant, as MDMA has known effects on appetite and weight. However, there were no differences in infant birthweight in this cohort and information on maternal weight gain during pregnancy was not available.

Finally, one child in the MDMA-exposed group was diagnosed by genetic testing with spontaneous, de novo (SALL1-mutation) Townes–Brocks syndrome after identification of physical anomalies at birth in ear, hand, and foot morphology (Powell and Michaelis, 1999). The only prior prospective follow-up of births of infants prenatally exposed to MDMA found a 15.4% increased risk in anomalies with cardiovascular and musculoskeletal anomalies predominant (McElhatton et al., 1999). Since the present reported case was documented as a spontaneous mutation, it would have occurred prior to conception and would not have been caused by maternal drug use during pregnancy.

Several limitations to this study should be considered. Pregnant women were voluntarily enrolled and MDMA and other drug use were identified by self-report. Participants thus may have had additional concerns for risk that precipitated their study involvement. However, both MDMA and non-MMDA users could be presumed to have been similar in that regard. Self-report of drug use may be unreliable, particularly when women may have concerns about fetal health and social stigma. Minimization of severity of drug use would serve to mask differences between groups, but functional outcomes in this study differed by amount of MDMA exposure, suggesting some validity to maternal self-report. Fetal exposure was almost entirely restricted to the first trimester, thus not generalizable to longer term exposure. The sample size for MDMA users was small. However, the sample did not contain a number of confounding factors seen in most recreational drug exposure studies, allowing greater power. Participants were from a wide range of socioeconomic status backgrounds including many from middle and high SES backgrounds, with average intelligence and education, employed, and primarily in married or stable partnered relationships. This study did not interview fathers about their drug use so it is not known if maternal MDMA use occurred in conjunction with her partner, although studies of use of other drugs, such as cocaine and marijuana, indicate a high correlation of use between partners (Grufferman et al., 1993). Future studies should also explore drug use in fathers immediately prior to conception as a risk factor.

Despite some limitations, the present study provides the first prospective developmental follow-up of MDMA-exposed infants and provides information on MDMA use in recreational drug users during pregnancy in a largely middle-class example. Findings of differences in sex ratio, and lower motor attainment and quality associated with heavier exposure to MDMA in the first trimester, suggest risk to the developing child. The occurrence of a rare genetic syndrome in the MDMA-exposed group is consistent with findings of anomalies in prior studies but cannot be attributed specifically to maternal drug exposure. Continued follow-up of the cohort to older ages is important for understanding whether these early motor differences persist or resolve.

Conflict of interest statement

Nothing declared.

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