In-utero exposure to the popular 'recreational' drugs MDMA (Ecstasy) and Methamphetamine (Ice, crystal): preliminary findings.

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Introduction

Chapters 8 and 9 outlined, in detail, findings on the emerging longitudinal outcomes of two of the most popular so-called recreational drugs: cannabis and cocaine. In contrast, there is far less extensive data on the impact on the developing human foetus of other increasingly popular synthetic amphetamine derivatives MDMA (3,4-methylenedioxy-N-methylamphetamine), commonly known as 'ecstasy', and Methamphetamine (MA; [2S]-N-methyl-1-phenyl-propan-2-amine) know as 'meth', 'ice' or 'crystal'. MDMA and MA are increasingly popular recreational drugs worldwide and the study of their effects on the development of human infants has only recently begun. This chapter reports what we currently know about the likely pattern of MDMA and MA use and the possible neuro-cognitive effects that MDMA and MA may have on mothers. We review the animal literature on the effects that MDMA and MA may have in utero and report the currently limited data on MDMA and MA effects on human infants.

Neurochemical effects

MDMA is a so-called 'synthetic' amphetamine and is a powerful, indirect, monoaminergic agonist which inhibits the reuptake and promotes the release of serotonin (5-HT), and to a lesser extent, dopamine (Green et al, 2003). MDMA also causes serotonergic neurotoxicity in laboratory animals (Morton, 2005). Neuroimaging literature suggests structural changes in adult recreational MDMA users and data show some broad parallels with the animal data on serotonergic changes, although it is an area of active discussion and debate (see: Buchert et al., 2003).

Amphetamine (racemic-B-phenylisopropylamine) is a powerful stimulant of the central nervous system. In adults it causes increased wakefulness, alertness, mood elevation, elation, and euphoria, and its effects are reported to be similar in some respects to those of cocaine. These effects are caused by stimulation of the release and blocking of reuptake of the neurotransmitters dopamine, norepinephine, and serotonin. Methamphetamine is an altered form of amphetamine with the addition of a methyl group. It is more readily absorbed into brain tissue than amphetamine (Barr et al, 2006) and importantly produces differential effects in prefrontal cortex and nucleus accumbens to the parent compound, which appears to result in a less inhibited net

reward effect (Shoblock et al, 2003). Taken together with a less negative peripheral sympathomimetic profile than amphetamine (see Iversen, 2006), this means that MA can be taken and tolerated at higher doses and, overall, is more addictive than amphetamine. While MA is often compared to cocaine in its effects, it has been suggested that MA may be more neurotoxic. The effects result from a cascading release of dopamine and also other monoamine neurotransmitters including norepinephine and serotonin (Kokoshka et al 1998). The release of dopamine occurs by a number of mechanisms including displacement of vesicles and inhibition of monoamine oxidase and through enhancing dopamine transport (DAT) across the plasma membrane, increasing dopamine concentration in synapses (see Scott et al, 2007 for a review). As with MDMA, research suggests that structural changes may occur in adult recreational MA users in specific neural pathways, specifically in dopamine rich fronto-striato-thalamo cortical loops (Cass 1997).

Prevalence in young adults

According to the British Crime Survey 24% of 16- to 24-year-olds in England and Wales report having used one-or-more illicit substances in the last year (Nicolas et al, 2007). Whilst males are more likely to use illicit substances than women, recent UK and EU data show that this gender gap is narrowing and that the experiences and drug-use patterns of young men and women are increasingly similar, even if the effects of the drugs may differ across genders (EMCDDA, 2005).

There is evidence of widespread use of MDMA by adolescents and young adults in the United States. The 2004 "Monitoring the Future" study indicated that rates of MDMA use had increased at accelerated rates from 1998 until 2001 reaching levels as high as 9.2% for twelfth graders and college students alike (Johnston, O'Mally, Brachman, & Schulenberg, 2005a). While rates of MDMA have decreased somewhat over a three year period based on the 2004 survey, 4% of twelfth graders report using MDMA in the past year and 7.5% reported lifetime use (Johnston, O'Mally, Brachman, & Schulenberg, 2005b).

In the UK and United States the use of MDMA has been associated with raves, all-night dance parties where ecstasy use is common, but in the UK and US MDMA is increasingly used in private social settings as well (Singer et al., 2004). NIDA's

Community Epidemiology Workgroup (CEWG), reporting on community substance use data in 2003 (NIDA-CEWG, 2004), indicated that MDMA use in the United States has spread beyond raves to a variety of urban, suburban and rural areas including greater use on college campuses. There has been an increasing effort to document the rave and other MDMA-use cultures in the United States, and to estimate rate of MDMA use both alone and in conjunction with other drugs. According to data collected from emergency room visits in the US, MDMA is most frequently combined with alcohol, marijuana and cocaine.

MA is also becoming one of the most dominant drugs of abuse, with an estimated 30 million users worldwide (United Nations Office on Drugs and Crime, 2004). There has, in particular, been a steep rise in production and use in South-East- and East-Asia (see McKetin et al, 2008). Use worldwide has increased from around 2.5% of adolescents and adults over 12 years of age in 1997 to around 5.5% in 2002. (United Nations Office on Drugs and Crime, 2004). Thus, MDMA and MA present serious public health concerns.

In the UK, the use of so-called 'recreational drugs' is commonplace and MDMA and MA are often taken together[1] and in temporal proximity with alcohol, tobacco, powder cocaine, cannabis and with other psychoactive substances (Drug Abuse Warning Network, 2000; Johnston et al., 2001;Yacoubian et al., 2003; Parrott, 2004; Scholey et al., 2004; Singer et al., 2004; Parrott, 2006), making it very difficult to establish their specific effects. Users may use one drug to counter the negative effects of another (see Miliani et al 2005) and there are also likely to be interaction effects, with these recreational drugs being differentially potentiated by alcohol and tobacco (see, for example, Ben Hamida et al., 2008).

Prevalence in pregnant drug-using women

The use of 'recreational drugs' is not limited to low socio-economic status (SES) groups and dependent users are not necessarily the same population of women who would regularly be using cannabis, powder cocaine, MDMA and MA. Many men and

[1] In some cases tablets are sold as 'Ecstasy' but in fact contain Methamphetamine, which is cheaper to produce (Kalasinsky et al, 2004; Quinn et al, 2004).

women in the UK who use recreational drugs do not also use ‘crack’ cocaine, heroin or other opiates, and many continue to hold down jobs and raise a family. These ‘non-dependent’/recreational users are less likely to be identified by health professionals unless they voluntarily disclose their use, as they do not present with obvious problems.

However the profile of use of drugs differs across countries adding difficulties in interpreting data. For example, Ho, Karimi-Tabesh, and Koren (2001) surveyed pregnant women, who contacted a drugs phoneline, in Canada and found that MDMA users were more likely to be younger, single, white, and be binge drinkers. They were more likely to have unplanned pregnancies , smoking and polydrug use were common and over a third of the women reported psychiatric problems. Thus, a range of factors need to be accounted for in these developmental studies and we need to take account of the differing social profiles across countries and cultures.

The accuracy of reported data on drug use is also an issue. In the UK, while some women may disclose their drug use during pregnancy to their midwife, , it is likely that many more do not, for fear they might be negatively judged or receive differential health care. Some may simply believe it to be a private issue and that the drugs they take are harmless. General information on the potential negative effects of drug taking is given to UK mothers but is not detailed except with respect to smoking and drinking, and this may contribute to a perception that the dangers are not great. Cannabis in particular is a drug which young women seem to consider less harmful than other illicit drugs (Pearson & Shiner, 2002) and levels of use in the UK may be high. In one UK survey around 5% of pregnant women were estimated to have used cannabis in pregnancy (Fergusson et al 2002).

However profiles of use of recreational drugs across different trimesters are likely to be uneven and different recreational drugs may have different profiles of use. Specifically some drugs may be more prevalent during early pregnancy. As MDMA and MA are more predominant in party/‘rave’ contexts and such parties are less likely to be attractive to women once pregnant, then levels of use of these drugs are likely to decline. However, early in pregnancy, prior to confirmation that they are pregnant, many young women will still be attending parties and may take a range of recreational

substances. Thus, the prevalence of MDMA and MA use in pregnant women in early pregnancy could be high.

Establishing levels of use in pregnancy through standard health networks may also be problematic. Anecdotal reports suggest that at NHS funded antenatal interviews in the UK, while midwives routinely ask questions on drug use, these are often passed over quickly and there is unlikely to be in-depth questioning. Thus, data on recreational drug use collected through these routes may under-report use, and may provide an unreliable picture of the combinations of drugs mothers are likely to expose their infants to across trimesters.

To address this issue the Drugs and Infancy Study (DAISY) study was set up. As the study was university based and outside of the National Health System (NHS), mothers who come forward seemed willing to disclose their full patterns of use. We interviewed women about their use of a wide range of legal and illicit drugs in their life up to pregnancy, in the year before pregnancy and over each trimester. We are also following up their infants to age two. This began in 2001 and to date we have recruited a cohort of 96 pregnant recreational drug-using women (see Moore et al, in press). Of these women 68 had used cannabis, 55 amphetamines, 54 MDMA, with the majority having smoked tobacco and having drunk alcohol in their lifetimes.

Our data has revealed that 35% of mothers who used MDMA at some point in their life before pregnancy also used MDMA in the first trimester and of those mothers who had used amphetamines in lifetime 9% used them at some point in the first trimester. However, only 4% of pregnant women used MDMA in the following trimesters and only one used amphetamines. We also found that the vast majority of MDMA users also used cannabis, and that the majority of women who used MDMA in the first trimester also drank, smoked or used cannabis in pregnancy, with around a third of the women continuing to use cannabis throughout all three trimesters.

The data confirms that, in the UK at least, infants of polydrug-using mothers are most at risk of MA or MDMA exposure in the first trimester, and that it is rare for users to take MDMA or MA in later pregnancy, but quite common for these women to continue taking cannabis and to drink and smoke at reduced levels (Moore et al, in

press). This highlights the need to consider the effects of drugs in combination, as in the real world women rarely use drugs in isolation.

Possible impact on the health and neuropsychological functioning of mothers

While there are some mixed reports on the impact of taking MDMA on daily living, chronic MDMA use has increasingly been shown to be associated with poorer general psychological health (Parrott, Sisk & Turner, 2000; Parrott et al., 2001; Thomasius et al., 2006): specifically with depression (MacInnes et a.l, 2001; de Win et al, 2004; Lamers et al., 2006) and increased anxiety (Lamers et al., 2006). As already outlined in other chapters, maternal depression and anxiety are known to be significant risk factors for infant development (see chapter 5).

Chronic MDMA use may also lead to impairments in aspects of everyday memory, prospective memory, frontal-executive processing, problem solving, decision taking and in social and emotional intelligence (Fisk et al., 2005; Fox et al., 2001, 2002; Reay et al., 2006; Rendell et al., 2007; Rodgers, 2000; Rodgers et al., 2003). These cognitive and social difficulties may act as contributory factors to adverse parenting possibly leading to reduced child-focused attention; poorer verbal and non-verbal communication and reduced sensitivity to the communications of their infants; and a higher risk of confusion or cognitive overload which could have an additional impact on affect and mood. Thus, from simple forgetting of tasks to generally poorer cognitive engagement and control, past and continuing drug use could significantly impact upon mother-child relations and therefore child outcomes.

While the exact nature of the long-term effect of exposure to MA on the adult brain is debated, there is consensus that MA has specific effects on episodic memory, executive functions, speed of processing motor skills, language, visuo-constructional abilities and other aspects of fronto-striatal and limbic related functioning; and clinical reports also suggest this population may be more distractible and inattentive (see Scott et al. 2007 for a review). Acute neuro-psychiatric effects of amphetamine and MA in adult users include agitation, tremor, hyperreflexia, irritability, confusion, aggressiveness, and panic states, among others. This is usually followed by fatigue and depression. Withdrawal effects can also be severe; and chronic injecting users

appear more susceptible to psychosis (McKetin et al., 2006). Again these effects will have a significant impact on women's capacities for caring for their infants.

In addition to long term neuro-cognitive effects, acute physical reactions to MDMA and MA have been recorded. MDMA specifically appears to contribute to rapid body temperature elevation (hyperthermia) and this may have subsequent effects on the liver, brain, and cardiovascular systems, sometimes sadly resulting in the sudden death of users (see Freedman et al, 2005; Green et al 2003; Parrott, 2005). While death is rare, these physiological effects, especially hyperthermia, could have significant negative consequences for fetal and pregnancy outcomes, and be additional mechanisms by which MDMA may alter pregnancy outcomes and infant development. MDMA can also lead to a demonstrated reduction in appetite and food intake in MDMA users during the week after use, and in some cases MDMA may be deliberately used as an appetite suppressant (see Curran & Robjant, 2006; Kobeissy et al, 2008; Turner et al., 1999). Poor nutrition is known to lead to poor outcomes during pregnancy (see Georgieff, 2007). MDMA and MA may also have an impact on maternal immunity which may also have adverse effects on pregnancy outcomes as yet unnoticed (see Connor 2004; Talloczy et al, 2008; Martinez et al 2009).

The use of MDMA and MA in combination with other drugs is also of particular concern, with many studies concluding that MDMA, amphetamines and cannabis are associated with more pronounced psychobiological problems in adult users (e.g. Milani et al 2000; Rodgers, 2000; Parrott et al. 2001). These adult neuro-psychobiological effects are likely to have important influences upon the behaviour of young women who are pregnant and, if use is continued throughout and beyond pregnancy, may have significant impact on their ability to care for their children once born.

Furthermore, while there is some debate, researchers (see Liechti et al., 2001; Allot & Redman, 2007) have suggested that females may be more vulnerable and show somewhat different MDMA effects than men, even allowing for body weight. Verheyden et al., (2002) found that female MDMA users tended to report mid-week feelings of depression, whereas males were more prone to aggression during the post-MDMA period. Milani et al (2004) and Ter Bogt and Engels (2005) have reported

gender specific patterns of psychobiological and psychosocial sequelae as a result of MDMA use and more recently Dluzen & Liu (2008) have reported a similar effect for MA, with women using MA commonly presenting with depression. Thus, to understand the impact of MDMA and MA on mothers it is important to consider these specific effects and to consider the developing literature on MDMA effects in adults in this light. Certainly the findings suggest that MA and MDMA-using mothers may be more at-risk for depression before, during and after pregnancy.

Medical outcomes of exposed infants

Animal studies of the impact of amphetamines have observed increased mortality, retinal eye defects, cleft palate and rib malformations, decreased physical growth and delayed motor development. There are also isolated reports of cardiac defects, cleft lip and biliary atresia after in utero exposure in human infants. Also reduced growth and increased fetal distress have been reported (See Billing et al. 1980; Catanzarite et al, 1995; Dixon et al., 1989; Eriksson et al ., 1978, 1981; Plessinger, 1998).

To date there are only a handful of studies that have examined the outcomes after maternal MDMA use during pregnancy in human infants. There is some suggestive, but inconclusive, evidence that MDMA use by mothers may have an impact on early cardiac and limb formation in human infants. A study by the Teratology Information Service for the National Institute for Public Health and Environment in the Netherlands has followed 43 cases (van Tonnigen-van Driel, Garbis-Berkvens, Reuvers-Lodewijks, 1999). Of 40 live born babies, one had a cardiac malformation, but it was noted that other substances were used by the mothers which were also potentially harmful in pregnancy.

Similarly, MDMA use in the United Kingdom has been tracked through the UK National Teratology Information Service, which by 2004 had collected prospective follow-up outcomes on 136 pregnancies (McElhatton, Hedgely, Thomas, 2004). Approximately 45% of these pregnant women were reported to have been taking MDMA only, with the remainder taking MDMA with other drugs of abuse during pregnancy, primarily amphetamines, cocaine, marijuana, and LSD. Women ranged in age between 16-36 years. Although this study is a case series, with associated

methodological limitations, reported prenatal MDMA exposure was found to be associated with a significantly increased risk of congenital malformations, particularly cardiovascular anomalies and musculoskeletal anomalies, 4-7 times higher than expected. Even after taking into account the higher prevalence of malformations associated with high risk pregnancies, there was a 2-fold increase of malformations associated with MDMA. However it should be noted that the accuracy of data on drug use was limited in this study, with the mothers being referred by health professionals after revealing that they had taken MDMA. They were not fully interviewed about their use of other drugs, and so it is not clear that these are genuinely sole-MDMA users. Indeed from our study and other reports MDMA is often used alongside other drugs and rarely used in isolation. Thus, these effects need to be considered in the context of the drug reporting methods used.

Neurocognitive effects of in-utero exposure in animals

While to date there is limited data on the effects of MDMA on the neuro-cognitive functioning of human infants. there is a growing literature of its effects in utero and post partum on the functioning of animals (for a review see Piper, 2007; Skelton et al 2008). One of the earliest studies was of one-day-old chicks (Bronson, Jiang, Clark, DeReuter, 1994). In this study it was found that prenatal exposure to MDMA produced effects such as distress vocalization, wing extension, tremors, flat body posture, loss of righting reflex, and convulsant-like kicking. Similarly, subsequent studies of MDMA exposure in foetal rats revealed subtle behavioural alterations to the pups and significant reductions in maternal (dam) weights (Omer, Ali, Holson, Duhart, Scalzo, Sikker, 1991). Meyer, Grande, Johnson, & Ali (2004) also found that neonatal MDMA exposure in rat pups led to significant reductions in serotonin levels in the hippocampus, the brain region associated with memory.

While some of these early studies of prenatal exposure failed to demonstrate any lasting neurobehavioural effects in rat pups (e.g. Aguirre et al, 1998; Colado et al., 1997), Vorhees and colleagues (Broening, Morford, Inman-Wood, Fukumura, and Vorhees, 2001) reported evidence that exposure to MDMA in rats during stages analogous to early and late third trimester human fetal brain development induced long-term learning and memory impairments. Further, while MDMA exposure had no effect on survival of neonatal rats, it did affect body weight gain during treatment.

Dose-related impairments on sequential and spatial learning and memory were noted with exposure on postnatal days 11-20, the developmental period in rats proposed to be equivalent to the third trimester in humans in terms of neuroanatomical development[2]. Similarly, MA exposure at postnatal days 11-20 in rats seems to lead to difficulties in water maze learning and may interfere with neurotrophic factors that are important for neuronal proliferation, survival and differentiation. Skelton et al (2007) found that MA exposure in rats leads to increases in brain derived neurotrophic factors (BDNF) in the hippocampus that may be responsible for water maze learning and memory problems reported in rats. These studies raise concerns about the impact of MA and MDMA during stages of brain development analogous to the late human foetal period.

However, the typical pattern of exposure to MDMA and MA based on our recent data from the DAISY study cited above (Moore et al, in press) suggests that in the UK at least the majority of prenatal exposure will occur in the first trimester when young women are still socialising at parties and before they are aware they are pregnant. Thus, work by Koprich and colleagues (Koprich, Chen, Kanaan, Campbell, Korlower, & Lipton, 2003) is perhaps most relevant. In their study, early prenatal exposure, in neonatal rat pups, equivalent to the first trimester was also sufficient to produce significant neurochemical and behavioural alternations. Pre-natally exposed MDMA animals had both reduced dopamine and serotonin metabolites in several brain areas, had reduced birth weight, increased locomotor activity, and showed a lack of habituation in a novel cage environment, suggesting persistent neurochemical and behavioural alternations following prenatal exposure.

The mechanism of MDMA-induced developmental effects has yet to be determined, but serotonin is known to have neurotrophic effects on neuronal development. Mazer et al., (1997) have shown that interfering with serotonin synthesis during the same developmental period as used by Broening et al (2001) can lead to long-term reductions in microtubule-associated protein (MAP-2), a synaptic marker. This suggests that the impact of MDMA is more on serotonin's role in connectivity rather than its role in neurotransmission. While the experiment of Mazer

[2] Note: see chapter 3, fig 1 for equivalent data on mice development in relation to human gestation.

et al., (1997) used the tryptophan hydroxylase inhibitor, p-chlorophenylalanine, and the experiment by Broening et al., (2001) used the serotonin-releaser, MDMA, both studies share the finding of long-term learning and memory impairments in the absence of long-term changes in brain serotonin levels.

Thus both MDMA and MA exposure in-utero may produce lasting changes in dopamine and serotonin systems and animal work suggests that both first and third trimester exposure may have an impact on the neurobiology of human infants with corresponding consequences for cognition, learning and social development.

Preliminary evidence of the neurocognitive effects of MA and MDMA on human infants

Predicting what the long term neuro-behavioural outcomes will be for human infants exposed to MA and MDMA in utero is not straightforward. The animal literature outlined above has largely been restricted to chicks and rats, and although there are some clear effects on motor functioning in animals exposed to large doses of MA and MDMA in utero, it is not clear to what extent these findings are generalisable to human infants. The frequency or size of dose in animal studies is likely to be larger than that administered to the typical human infant, and the human neurological system clearly differs markedly from that of a rat or a chick.

Furthermore, literature that has explored the effects of MA and MDMA exposure on the adult human brain, while useful in determining how exposure might affect maternal behaviour, may not allow us to clearly predict what the effects of exposure will be on the developing *infant* brain. The developing infant brain has a large degree of plasticity and in the initial stages of neuronal development cognitive functions and corresponding brain structures and pathways are not as localised and specialised as in adulthood (see Johnson, 2003). Thus the elements of the serotonergic and dopamine systems that may be vulnerable to MA and MDMA-effects in adults may not necessarily be those that are affected in infancy, nor, even if the same pathways are involved, does this necessarily mean that the same insult will lead to the same outcomes.

It is reasonable to postulate that children with a history of fetal MA or MDMA-exposure are more likely to perform poorly on overall measures of cognition, language, emotional functioning, and behavioural competence, and may show differences in motor skills reflecting, for example, the problems found by Bronson et al (1994) in chicks. Further, if it is safe to extrapolate from the adult literature and literature on the additive effects of polydrug use, we might also predict that there may be particular deficits in neuropsychological functions. In particular, polydrug use may particularly impact on developing executive functions, attentional processes, visual-spatial and language skills. Note, however, that in infants of polydrug using women, these effects may not be distinguishable from those reported for cannabis, although there could be an additive or interaction effect of polydrug use.

While the neuro-cognitive effects of MDMA and MA on human infants are only now being researched, there is some limited longitudinal data on the impact of unmodified amphetamine on the neuro-cognitive development of exposed infants. Billing and colleagues followed infants from birth through to 14 yrs. (See Billing et al, 1980; 1985; 1988; 1994; Cerneraud et al 1996; Eriksson et al., 1981, 1989). In the first few months infants shown increased drowsiness, and infants exposed to amphetamines throughout all trimesters of pregnancy, showed more social communicative problems at age one (Billing et al, 1980). By age eight, exposure was found to be related to later aggressive behaviour and problems with peers. At age fourteen, children showed problems with maths, language and physical activities (Cernerud et al 1996). It must be noted however that this study was limited in sample size, lacked a control group and it was not possible to separate out MA effects from those of other drugs. Also, as noted above, the action of amphetamines and methamphetamine differ in the intensity of their effects.

There have been two MRI studies of children exposed prenatally specifically to MA. These have examined possible structural changes and behavioural functioning (Smith et al; 2001; Chang et al 2004). These studies examined a small sample of 7-8 year olds (n = 13) exposed prenatally to methamphematine and other substances (alcohol and tobacco) and a control group of unexposed children. Smith et al, (2001) used proton magnetic resonance spectroscopy to evaluate neurochemical alterations and found possible alterations in cellular energy metabolism in the basal ganglia of

the methamphetamine exposed group. Chang et al (2004) performed volumetric analysis and revealed bilateral reductions in the volume of the globus pallidus, putamen and hippocampus. In contrast no differences were found in the thalamus, midbrain or cerebellum. However the study did not control for polydrug use so the specific MA effect may not be determined.

More recently, two NIDA (NIH) funded studies have begun in the US and UK to examine the impact of MA and MDMA. The DAISY study, already referred to, has directly recruited a cohort of over 100 polydrug and MDMA using pregnant women and is shortly to publish data on infant outcomes. The other study is the IDEAL study (see Smith et al, 2006). This is a multi-site longitudinal study of MA and has screened an initial cohort of almost 14,000 women. Around a fifth of this sample drank alcohol, around 6% used cannabis and the incidence of MA use at some point in pregnancy was around 5% (see Aria et al 2006). From this larger sample they have recruited 74 MA users and 92 comparison women into a prospective longitudinal study.

The infants born to the mothers recruited who took MA were 3.5 times more likely to be small and to have lower birth-weight-for-gestational-age even controlling for tobacco and alcohol effects (Smith et al 2003) and initial findings of the impact of MA on newborn (up to 5 days old) neurological and motor functioning indicate some dose-dependent effects on infant arousal (Smith et al 2008). Infants were assessed using the NICU Network Neurobehavioural Scale (NNNS; Lester & Tronick, 2004) and MA exposure in the first trimester was related to lower arousal, more lethargy and elevated stress indicators (those behaviours that are also typically associated with abstinence/withdrawal in opiate exposed infants). Also, MA exposure in the third trimester related to poorer quality of movement.

These neonatal effects were also found alongside a higher prevalence of depressive symptoms in the MA-using mothers (Paz et al 2009) which in turn were associated with decreased arousal and increased stress in the infants; although this factor did not add to the overall direct MA effect. Thus, high levels of MA use may be impacting directly on neurological development and also indirectly via the impact of maternal depression. This study is ongoing and the longer term effects of MA on neurological functioning are yet to be determined.

Conclusions

Although studies are limited, there is some emerging evidence for the teratogenic effects of MA and MDMA from both preclinical and human studies and the IDEAL study has begun to find some specific effects of MA in the infant period. In addition animal studies suggest that MA or MDMA-use by mothers will impact on the foetal seretonergic and dopamine systems. However, extrapolating from animal effects to effects in human infants is not simple.

Data from the DAISY study to date show that in the UK MDMA exposure is likely to predominantly occur in the first trimester, and that this exposure is unlikely to occur in isolation but alongside other drugs. Animal models need to be further developed to reflect these likely patterns of use, so we can better extrapolate these findings to human *in utero* development. These drugs may not have a simple additive effect in utero but may interact in their effects in ways yet to be determined.

What is clear is that, to understand the ramifications of foetal exposure to these increasingly popular drugs, there needs to be more prospective longitudinal studies of polydrug users, with adequate sample sizes that allow the statistical control of the many confounding variables. However our experience in the UK is that it is difficult to recruit pregnant recreational drug users via the typical health service routes and future studies will need to use a variety of recruitment techniques to gain a large enough sample to consider a range of extraneous factors.

Studies also need to use a broad number of outcome measures sensitive to neuropsychological dysfunction, similar to those outlined in chapter 9 in studies on cannabis. These studies need to have extended follow-ups into late childhood to be sure of capturing the potential long term effects. Investigations of the indirect effects of maternal psychological status and caretaking behaviours are also needed to provide information essential to the development of effective maternal drug treatment and child intervention programs. The examination of interaction effects of various drugs is key. The DAISY and IDEAL studies are longitudinally documenting outcomes of a prospectively recruited sample of exposed infants whose prenatal exposure has been

characterized through maternal biologic and self-report measures throughout pregnancy, and whose care giving environment, including maternal psychological status, has been characterized post-natally. Findings from the IDEAL study are now beginning to be published and we also will be reporting infant outcomes from the DAISY study in the near future.

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