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STATE-OF-THE-ART

Amphetamines, the pregnant woman and her children: a review

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The objective of this study is to review and summarize available evidence regarding the impact of amphetamines on pregnancy, the newborn infant and the child. Amphetamines are neurostimulants and neurotoxins that are some of the most widely abused illicit drugs in the world. Users are at high risk of psychiatric co-morbidities, and evidence suggests that perinatal amphetamine exposure is associated with poor pregnancy outcomes, but data is confounded by other adverse factors associated with drug-dependency. Data sources are Government data, published articles, conference abstracts and book chapters. The global incidence of perinatal amphetamine exposure is most likely severely underestimated but acknowledged to be increasing rapidly, whereas exposure to other drugs, for example, heroin, is decreasing. Mothers known to be using amphetamines are at high risk of psychiatric co-morbidity and poorer obstetric outcomes, but their infants may escape detection, because the signs of withdrawal are usually less pronounced than opiate-exposed infants. There is little evidence of amphetamine-induced neurotoxicity and long-term neurodevelopmental impact, as data is scarce and difficult to extricate from the influence of other factors associated with children living in households where one or more parent uses drugs in terms of poverty and neglect. Perinatal amphetamine-exposure is an increasing worldwide concern, but robust research, especially for childhood outcomes, remains scarce. We suggest that exposed children may be at risk of ongoing developmental and behavioral impediment, and recommend that efforts be made to improve early detection of perinatal exposure and to increase provision of early-intervention services for affected children and their families.
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Introduction

As amphetamines (alpha–methyl–phenethylamine) continue to be widely misused throughout the world and there is growing concern about the increasing number of exposed babies from maternal use in pregnancy. In this review, we consider existing evidence regarding the impact of amphetamines during the perinatal period. We include an historical overview of the drug and its pharmacodynamics, contemporary addiction treatments of both woman and child, as well as a summary of the demographics of amphetamine-using women of childbearing age. We also consider placental and fetal transfer of the drug and its effects on the newborn infant. Finally, this review discusses the perinatal management of known amphetamine-using mothers, along with indications and utility of toxicological diagnosis of exposure in the mother and infant, and the pros and cons of breastfeeding for affected mother/infant dyads.

Amphetamines

Amphetamines are synthetic psychostimulants that were first synthesized in 1887 by the Romanian chemist, Lazãr Edeleanu, from the naturally occurring central nervous system stimulant, phenylethylamine.[1] These drugs increase wakefulness and attention, and decrease appetite and fatigue. Various substitutions of chemical moieties to its phenethylamine core result in derivatives with different clinical effects, many of which have been marketed in various forms over the years[2] for different clinical purposes (Table 1).

The effects of amphetamines are mediated through the modulation of dopamine, serotonin and norepinephrine. These are key neurotransmitters in the central nervous system that are highly involved in the control of reward pathways in the mesolimbic and mesocortical systems. Table 2 provides a summary of the pharmacodynamics of amphetamines.

Amphetamine-users become more alert, gain increased concentration, energy, self-confidence and sociability. Users need less sleep and food, but may also become irritable and aggressive,

Table 1 The history of amphetamines

Year	*Chemical structure*	*Purpose*	*Comment*
1887 Romanian chemist Lazăr Edeleanu	Amphetamines (alpha–methyl–phenethylamine)	Unknown	First synthesized from naturally occurring CNS stimulant phenylethylamine[1]
1920 Japanese chemist, Akira Ogata[2]	MA; MDMA; phentermine	Unknown	Substitution of the amino group enhances stimulating effect[3] Replacing the methyl group in position α reduces stimulating and hallucinogenic actions, but has no effect on empathogenic or anorexic effects[4]
1927 Psycho-pharmacologist Gordon Alles	Amphetamine	Used as a replacement for ephedrine	—
1932–1933	Amphetamine (Benzedrine)	Marketed in the form of an inhaler for decongestant purposes[2]	USA Food and Drug Authority banned Benzedrine inhalers and limited amphetamine prescription use in 1965, because of its addictive properties
1939–1945 (World War II)	Amphetamine	Treated combat fatigue and increased alertness in soldiers	Soldiers became quickly dependent on the drug and needed prolonged rest to recover from its use[2]
1971	Amphetamine	Placed on USA Controlled Substances Act in 1971[5]	Became a class II drug (CNS stimulant) under the Convention of Psychotropic Substances (1971)[5]
Current	D-amphetamine, methylphenidate and atomoxetine	Only current legally sanctioned indications for use	Treatment of ADHD, traumatic brain injury, narcolepsy, postural orthostatic tachycardia syndrome, chronic fatigue syndrome[4] and post-traumatic stress disorder[6]
	Illegally manufactured amphetamine-type substances	Supply and demand for illicit drug trade	The United Nations estimate that approximately 50 million people in the world are current methamphetamine users[7,8]

Abbreviations: ADHD, attention deficit hyperactivity disorder; CNS, central nervous system; MA, methamphetamine; MDMA, methylene-dioxymethamphetamine.

develop delusions of grandiosity, power, superiority, paranoia and overt psychosis with hallucinations and delusions. Table 3 shows a range of adverse effects that have been described in existing medical literature.

Amphetamine withdrawal may result in profound fatigue and somnolence. Users may become extremely depressed and symptoms may last for months, especially in chronic and heavy users.[23] Magnetic resonance imaging studies show that methamphetamine (MA) use, for example, causes cerebral microstructural abnormalities in the right prefrontal, corpus callosum and mid-caudal superior corona radiata, which are pathological findings that can be associated with depressive and generalized psychiatric symptoms.[24] Abstinence may lead to agitation, severe anxiety and suicidal ideation.[25] These problems may also affect patients who are treated with amphetamines for clinical problems.[26]

Amphetamine-users rapidly develop tolerance and dependence. Chronic methylene-dioxy-MA users, for example, may require 10 to 25 tablets to achieve similar effects to 2 to 3 tablets for novice users.[27] This may be because of impaired release of neurotransmitters, such as serotonin, after chronic drug exposure.[28] However, the eventual expression of tolerance depends considerably on daily drug dose and the interval between doses.[29] Polydrug use (the use of multiple drug classes), a common problem in amphetamine-users, may greatly enhance the risk of adverse effects like overdose. This may result from both the intentional and unintentional consumption of additional agents that augment physiological instability, for example, sedatives like benzodiazepines and alcohol to temper and extend the effects of amphetamines,[30] or toxic contaminants that are incorporated into amphetamines during manufacture.[31]

Treatment for addiction

Amphetamine users are highly unlikely to engage or stay in treatment programs, because they may not perceive their drug use as being problematic.[32] They may think that treatment programs are 'opiate-centric' and not relevant to their needs. As a result, amphetamine users are known to have a tendency to self-detoxify with both licit and illicit substances.[33] There are no receptor blockers for amphetamines akin to naloxone or replacement therapies like methadone and buprenorphine for opiate dependence, but there is increasing promise that other forms of stimulants may be used as a substitute to assist individuals by reducing cravings and withdrawal symptoms, in a concept similar to the use of methadone for opiate dependence. Few of these studies have produced clinically significant effects and further study to refine the doses or to examine larger patient groups is needed. Galloway *et al*.[34], for example, randomized 60 MA-dependent adults to 60 mg of sustained d-amphetamine or placebo for 8 weeks and found no decrease of MA use in the treated group, which had

Table 2 Pharmacodynamics of amphetamines

	Action	*Effect*	*Comment*
Amphetamines	Enhances release of dopamine from the synaptic vesicle[9]	Increases the concentration of dopamine in the cytosol of pre-synaptic neurones	—
	A substrate for the specific neuronal synaptic vesicle uptake transporter adrenergic vesicular monamine transporter	Dopamine release into the cytosol Interacts with the dopamine transporter Reverses dopamine transport	Dopamine readily oxidizes in the cytosol, leading to oxidative stress and autophagy-related degradation of dopamine axons and dendrites.[10]
	Acts on tyrosine hydroxylase, which synthesizes the dopamine precursor L-DOPA and causes some blockade of DAT	Inhibits monoamine oxidase, an enzyme responsible for dopamine breakdown in the cytosol Enhances dopamine synthesis	Similar mode of action to cocaine, amphetamine releases more dopamine than cocaine or other addictive drugs[11]
	Reverses the action of the serotonin transporter, SERT, in specific regions of the brain, for example, the mesocorticolimbic projection	Alters the function of glutamatenergic pathways from the ventral tegmental area to the prefrontal cortex[12] Blocks norepinephrine reuptake[4]	—
Both amphetamine isomers, levo- and dextro-amphetamine	Binds to monoamine transporters	Increase extracellular levels of neurotransmitters	D-amphetamine may act primarily on dopaminergic systems, whereas the l-isomer may act on norepinephrine.[13]

significantly reduced withdrawal and craving scores. Shearer *et al*.[35] randomized 38 MA users to 200 mg per day of modafanil and 42 others to a placebo for 10 weeks, and found no differences in treatment retention, medication adherence and behaviors like craving or severity of dependence. However, modafanil-compliant MA users who did not use other agents and who sought counseling had better outcomes with statistically significant reductions in systolic blood pressure and weight gain, compared with placebo-treated users. Other agents that may show promise include the antidepressants bupropion,[36] fluoxetine[37] and imipramine,[38] but the patient populations in which these agents are effective appear to be relatively select (e.g., males)[36] and restricted to those who actively seek intensive counseling.[34–38]

The prevalence of amphetamine use in women of childbearing age

There are two types of amphetamine users—those who are legally prescribed amphetamines for medical reasons, and the non-medical users. The prevalence of amphetamine use, whether legal or illicit, is a substantial global problem that affects almost all population age groups. Attention-deficit hyperactivity disorder, for example, may affect three to seven million children between 4 and 13 years of age in the United States alone,[39] and more than 75% of these children may be prescribed amphetamines at any one time.[40] It has been suggested that up to 5% of adults may have attention-deficit hyperactivity disorder,[41] resulting in a substantial number of women of childbearing age, who could have attention-deficit hyperactivity disorder and who could require amphetamine treatment.

The major concern, however, is about those who use illegal forms of amphetamines, for example, MA. The United Nations estimate that almost 53 million people in the world are current MA users,[7,8] and amphetamines are the second most commonly abused illicit drug in the world after cannabis, especially in developing regions of the world.[7,8] These numbers, however, are most likely gross underestimations due to a high incidence of non-disclosure,[42–44] particularly amongst highly functioning users. Indeed, anonymous surveys from developed nations such as Australia show that 2.1% of the population (or about 400 000 persons) above 14 years of age admitted to using amphetamines in the previous year.[44]

Most amphetamine users are men between 20 to 29 years old.[44,45] In Brazil, for example, differences in drug consumption between sexes in a cohort of university students are highest with amphetamines (1.1% females vs 3.2% males had taken the drug in the previous 30 days).[45] Unfortunately, there are no definitive numbers of amphetamine-exposed pregnant and lactating women. This may require extrapolation from general population data, medical chart record review[46] or linkage analysis between health databases.[47] Further study is certainly required to determine the true prevalence of illegal amphetamine exposure in the perinatal period, so that appropriate management can be given to the mother and her family. Unfortunately, it appears that perinatal amphetamine drug use is increasing worldwide. In the United States, for example, admissions for pregnancy-related MA abuse increased from 8% of federally funded admissions in 1994 to 24% in 2006, a higher rate of admission than for non-pregnant women (12%) and for men (7%).[48] More recent single-center Australian studies have demonstrated increase of between two[47] to three times[49] of amphetamine use in known pregnant drug users, whereas

Table 3 Evidence of amphetamine-related drug effects and implications

Reported in (author)	*Drug effect*	*Implication*
Zorick *et al*.[14]	Psychosis	Difficult to treat and may occur intermittently for months to years after abstinence
Volkow *et al*.[15]	Increased libido	May lead to risky sexual behavior and susceptibility to blood-borne infections and other complications
Brown *et al*.[16]	Tachycardia, tachypnea, febrile, diaphoresis and seizures	Seizures may occur, usually within 24 h of exposure and may be exacerbated by sleep deprivation
Hung *et al*.[17]	Ischemic heart disease	This is a rare but increasingly important complication caused by coronary vasospasm
Westover *et al*.[18]	Acute myocardial infarction	It was estimated that amphetamine abuse was responsible for 0.2% of cases of acute myocardial infarction in the state of TX, USA
Callaghan *et al*.[19]	Parkinson's disease	Chronic users, especially of methamphetamines, are at an almost triple risk of developing Parkinson's disease because of dopaminergic neuronal depletion
McCann *et al*.[20]	Neurological deficits—short-term memory, executive function and manual dexterity	Symptoms may persist even after protracted abstinence
Saini *et al*.[21]	Xerostomia and caries	Condition possibly due to a combination of decreased salivary flow and poor attention to oral hygiene
Nabet *et al*.[22]	—	An important problem in pregnant women, because poor oral hygiene has been implicated in the pathogenesis of adverse perinatal outcomes, such as premature labor and preeclampsia

heroin use has decreased or remained static.[49] These results are reflected in larger multi-center studies. A chart review of known perinatal drug users birthing in metropolitan hospitals of NSW, Australia, showed that the proportion of amphetamine use amongst these women increased from 21.4% in 2004 to 25.8% in 2007,[50] despite a decrease in general-population amphetamine use, from 3.4 per 100 population in 2004 to 2.7 per 100 population in 2007.[51]

Characteristics of amphetamine using mothers

There is little information on the characteristics of mothers using prescribed amphetamines for medical or recreational purposes. Mothers with attention-deficit hyperactivity disorder[52] and narcolepsy,[53] who need to take amphetamines for their medical disorders, may not be different to parents with other chronic illnesses, who may find it difficult, because of the stress of their disease, to maintain discipline, to set boundaries or to cope with the delegation and completion of routine chores.[54] Such mothers (and their families) require support and education, for example, with respite care or strategies to help them cope with the stress of parenting, especially during the demanding toddler years, as disease exacerbation has been shown to result in a withdrawal of parenting involvement within these families.[55]

Most data arise from studies of known users of illicit forms of amphetamine, notably MAs. Pregnant users of illicit amphetamines, regardless of their country of origin, are more likely to be socially deprived, even when compared with other drug users.[46,56–58] They are usually younger, less likely to seek timely antenatal care, have lower household incomes, less likely to be privately insured or to have partner and family support. This group of women also receive less formal education and are more likely to be involved in marginalized lifestyles involving criminal activity, homelessness or domestic violence. Co-morbid psychiatric morbidities, notably depression and anxiety, are twice as common than even other drug-using mothers.[46,59] This is of great concern, as psychiatric co-morbidities may significantly impair parenting skills[60] and childhood neurodevelopment.[61,62]

Placental and fetal transfer of amphetamines

Amphetamines are undoubtedly transferred across the maternal-fetal circulation as amphetamines and their byproducts are easily detectable and quantifiable in the umbilical cord,[63] the placenta[64] and the amniotic fluid.[65] The lack of a capillary network, and therefore the absence of an endothelial barrier on the maternal side of the placenta, facilitates transfer of nutrients and oxygen, and also of substances that are ingested by the mother, including drugs.[66] Exposure to amphetamines, however, increase the risk of placental hemorrhage, because amphetamines mediate serotonin-associated platelet activation,[67,68] uterine contraction[68] and may be the cause of preterm labor that is commonly associated with amphetamine exposure.[68]

It is noteworthy that animal studies report a rapid (<30 s) transfer time of amphetamines from administration to pregnant ewes to their fetuses. Fetal drug levels gradually become higher than maternal drug concentrations because of prolonged fetal drug elimination times. The highest drug concentrations are found in fetal lungs, followed by placenta, kidney, intestine, liver, brain and heart.[69] Amphetamines may be detected also in amniotic fluid for up to 7 days after intra-peritoneal administration to pregnant rats. Amniotic fluid levels have been shown to correlate well with brain amphetamine levels and may be a potential surrogate marker of cerebral exposure to the drug.[65,70]

Fetal effects

Fetal amphetamine exposure has not, so far, been proven to be definitively teratogenic. Drugs such as amphetamines, alcohol and nicotine all reduce folic acid uptake in primary culture of human cytotrophoblasts. This, in itself, may be potentially fetotoxic.[71] Amphetamines are noted to preferentially affect cardiac and neural cells. Methylene-dioxy-MA, for example, reduces the number of beating cardiomyocytes and neurons, and decreases neuronal differentiation in cell cultures.[72] In animal studies, MA administration to pregnant rats changes alpha- and beta-major histocompatibility complex mRNA expression pattern in fetal and neonatal hearts, resulting in abnormal cardiac development and myocardial damage.[73] There is no human evidence of amphetamine-associated cardiotoxicity and this deserves further study, considering the severe implications of *in-utero* myocardial damage. Amphetamine-exposed infants, however, are often noted to have smaller head circumferences, even when compared with other drug-exposed newborn infants,[74] and this may be the result of fetal serotonin depletion, leading to reduced total dendritic length and altered dentate granule cell morphology, especially at the synaptic level.[75]

Regardless of this, no definitive structural abnormality has been associated with perinatal amphetamine exposure even with extremely large doses of the drug. A woman who was treated with large amounts (140 mg, range 100 to 180 mg) of dextroamphetamine sulfate (Dexedrine) for narcolepsy for 10 years delivered a healthy term infant at 3.63 kg without any symptoms of withdrawal and intoxication, or evidence of structural abnormalities.[76] There are case series and reports of various forms of congenital abnormalities associated with amphetamine – exposure, but again, because of the many inevitable confounding factors, a definitive link is hard to establish. A prospective follow-up of 136 babies exposed to *in-utero* methylene-dioxy-MA found a 15-fold risk of developing any congenital defect (odds ratio 15.4; 95% confidence interval 8.2 to 25.4), a 26-fold risk of cardiovascular anomalies (odds ratio 26; 95% confidence interval 3.0 to 90.0) and 38-fold risk of musculoskeletal anomalies (odds ratio 38; 95% confidence interval 8.0 to 109.0),[77] but similar problems have also been noted with vasoactive and recreational agents[78] that disrupt vascular supply to the developing gastrointestinal tract.[79] Isolated reports of conditions, such as biliary atresia[80] and bifid exencephalia,[81] have not been confirmed in animal studies.[82,83]

Pregnancy outcomes

Whether amphetamine exposure causes increased fetal loss is uncertain because of the difficulties in establishing drug-use disclosure[43] and the often accompanying adverse confounding factors, such as polydrug use, maternal domestic stress[58] and malnutrition.[84,85] There are, however, reports of fetal and infant death where amphetamines were detected in fetal bloods at comparable concentrations to maternal levels.[86] Dearlove *et al*.[87] reported on a case in which a 29-year-old woman took 500 mg intravenous amphetamine and presented shortly after with acute abdominal pain at 34 weeks gestation. A still-born female was delivered with a cord amphetamine concentration of 0.11 mg l^{-1} and plasma concentration of 0.09 mg l^{-1}, and fetal death was attributed to amphetamine abuse. Reports of increased rates of perinatal mortality and prematurity stem predominantly from small studies[88,89] and have not, to date, been substantiated from population data comparing known amphetamine users with the general parturient population.

When compared with pregnant women from the general population, repeated studies show that known amphetamine users are significantly more likely to have minimal antenatal care and be at higher risk of complications, such as hypertension and placental abruption.[54,56,89] This may be a consequence of health care access, and the risk of complications may be reduced if the women had easier access to perinatal services. LaGasse *et al*.,[90] for example, found little difference in terms of antenatal care between MA users and non-users in New Zealand, in contrast to America. Regardless, illicit amphetamine users are undeniably disadvantaged when seeking antenatal care, because a significant proportion are affected by adverse psychosocial circumstances, such as various psychiatric co-morbidities and domestic problems[46] Targeting these issues, for example, engaging the women in psychiatric services may increase the rate of antenatal engagement.[60]

Neonatal effects

Low birth weight is a consistent finding in known amphetamine-exposed infants[46,54,55,88,91] when compared with population norms. The cause of this is uncertain, because pregnant amphetamine-using mothers are again exposed to multiple factors that could retard fetal growth. However, Delsing *et al*.[92] compared 91 opiate and 37 amphetamine-exposed infants for deviations from normative fetal growth and found unexpectedly that amphetamines increased head and abdominal circumferences, as well as femoral lengths in the third trimester, even in the presence of nicotine exposure. In the ovine model, amphetamines independently increase maternal and fetal blood pressure, which restricts fetal nutrition, oxyhemoglobin and arterial pH levels.[69,93] This may restrict fetal growth, as shown by the delivery of significantly lighter and shorter offspring,[94] with disturbed myelination, especially in the optic nerve[95] of animals injected with perinatal MA.

Unless there are other drugs or extenuating clinical circumstances involved, amphetamine-exposed infants, especially those of recreational users, may not be identified when they are assessed for signs of withdrawal with commonly used neonatal

withdrawal scoring systems.[96,97] These are opiate-centric scoring systems that have been validated for use in term or near-term infants. However, they are often erroneously used for assessing amphetamine-exposed infants, because there are no other suitable assessment scales.[46] It must be noted that the most common presentation of infants exposed to recent amphetamine use is lethargy, somnolence and poor feeding,[46,56,57] in a presentation similar to an adult user who experiences profound fatigue and anorexia after an amphetamine 'crash'.[98] Indeed, both mother and infant may be difficult to arouse after birth. Examination tools, such as the neonatal intensive care unit network Neonatal Behavioral Scale, was found by LaGasse *et al*.[90] to be useful in correlating the effects of amphetamines on physiological adaptation in exposed infants, which were noted to be dependent on the timing and magnitude of exposure. First trimester resulted in greater total stress/abstinence and physiological stress, whereas third trimester and heavy use with increased lethargy and hypotonicity. Certainly, further work is required to establish pragmatic assessment scales for amphetamine-exposed infants, so that those at risk of intoxication or withdrawal can be easily identified and treated as necessary. Using opiate-centric scores may lead to misdiagnosis and under-treatment, especially when health providers are focused on identifying symptoms and signs that are similar to opiate withdrawal.

Even though some amphetamine-exposed infants present with agitation and tachypnea[56,57] the majority require only minimal supportive treatment, for example, gavage feeding for about a week. Few have been shown to need pharmacological treatment.[46,56,57] Thaithumayon *et al*, for example, compared 173 amphetamine-exposed with 33 heroin-exposed infants and found that drug-withdrawal symptoms occurred earlier (10.3 ± 7.5 vs 21.5 ± 16.5 h) and less frequently (2.2 vs 93.9%) in the former. None of the amphetamine-exposed infants required pharmacological treatment and most recovered within 1 week.[57]

Currently, there is no receptor-appropriate treatment for neonatal amphetamine withdrawal or intoxication that is similar to morphine for opiate withdrawal.[99] Symptoms that cannot be controlled with supportive measures (e.g., gavage feeding, ventilator support) may require treatment with phenobarbitone, an anti-epileptic medication, and sedative. Seizures have been reported in adults[100] and children,[101] but not in newborn infants. The indications for phenobarbitone in neonatal amphetamine exposure are not well defined, being based, in most instances, on assessments validated against opiate effects in term or near-term infants. Phenobarbitone can be given orally (or intravenously if the infant cannot tolerate oral feeds). Weaning is also subjective and currently without evidence.[102] Caution must be used because the long-term effects of drugs such as phenobarbitone has been shown to disturb cell proliferation, survival and neurogenesis in animal studies.[103] Finally, amphetamines are hepatotoxic in adults,[104] the mechanisms of which are unclear.[105] Similar problems have not been reported in the newborn infant, apart from an increased risk of prolonged but self-resolving conjugated jaundice.[106]

Perinatal management of the known amphetamine-using mother

Many amphetamine users are potentially at risk of being deeply entrenched in a drug-using lifestyle,[26] prioritizing drug-using behaviors over their own health and social needs. Almost 60% of this population may be affected with multiple psychiatric co-morbidities,[60] as well as social problems, such as homelessness, risk of domestic violence or incarceration, which are even more prevalent than other known drug users.[46] As there are currently no replacement therapies for amphetamine dependence, the pregnant amphetamine user must be encouraged to moderate and cease drug use, but this may be an unrealistic expectation. A priority in prenatal care for the known amphetamine user is to ensure that she has adequate shelter and nutrition, that co-existing psychiatric morbidities are optimally treated, and that she is encouraged to attend regular antenatal care, which is, unfortunately, even less frequent than other known drug users.[106]

Toxicological diagnosis of amphetamine exposure in the mother and infant

Drug screening may not yield substantially more useful information beyond that obtained from carefully administered and non-punitive drug and alcohol histories, but this depends considerably upon the rapport between the patient and the attending health-care team. A major dilemma is the diagnosis of first trimester amphetamine exposure. Neither neonatal urine nor meconium (the first neonatal stool), the two most common newborn matrices used for drug testing, are able to detect early gestational drug exposure. Meconium is formed and stored from 16 to 20 weeks of gestation, whereas fetal (and neonatal urine) continuously excretes maternal drugs so that amphetamines may not be detectable in neonatal urine after 3 to 4 days of postnatal age because of its short half-life (i.e., 16 to 31 h).[107] Detection of amphetamine exposure using these two matrices depends on the timing of last maternal ingestion, and amphetamine metabolites may not be present in urine after 2 to 3 days of maternal abstinence, as is the case with most recreational amphetamine users.

Maternal labetalol may create false-positives on urine testing for amphetamines.[108] Meconium, however, is a very stable matrix and provides a serial and quantitative picture of maternal drug use from the 16th week of gestation.[109] However, meconium toxicology is usually only performed in reference laboratories and therefore is not universally available for diagnosis. False-positive results from meconium testing may be as high as 43% for some drugs.[110] Furthermore, obtaining 0.1 g (the minimum weight of dried

meconium required for standard panels of drug tests) may be quite difficult, even with serial collections of stools.

Other biological matrices that show diagnostic promise are hair,[111] nails,[112] amniotic fluid,[65] the placenta[64] and the umbilical cord.[65] Currently, the use of these matrices is limited by technical and practical feasibility, as processing and analytic techniques have not been standardized. For example, it is difficult to obtain sufficient hair for analysis (usually a pencil-width is required) and preparation requires specialized forensic laboratory expertise and equipment. Hair can also be contaminated by atmospheric products[111] and subject to question for its reliability. Drugs (e.g., cocaine) have been detected in the nails of deceased subjects, but again, preparation is difficult and not of practical use.[112] Amniotic fluid is difficult to obtain reliably, unless through an organized procedure like an elective cesarean section or amniocentesis. The placenta and umbilical cord shows promise as readily available products for testing. The umbilical cord, in particular, is formed during the first 5 weeks of gestation[113] and is freely available at birth. Further investigation into the use of the cord as a standard testing tool for perinatal amphetamine exposure is required.

Breastfeeding

Amphetamines inhibit prolactin release and may reduce breast milk supply.[114] Abstinent amphetamine users may be hyperprolactinemic.[14] Breastfeeding should not be encouraged during active illicit amphetamine use for several reasons.[115] Illicit amphetamine users may have erratic drug-use habits that severely impair the mother's ability to parenting, for example, excessive somnolence or erratic behavior. The effects of discouraging breastfeeding in this situation on maternal-infant attachment have not been evaluated. Realistically, some women may continue to breastfeed, despite medical advice, and therefore, all known amphetamine users, whether current or otherwise, must be educated to seek active support while they are feeding, in case they develop significant adverse effects from the drugs that could place their infants at risk.

The case for breastfeeding, although women are taking prescribed amphetamines, is less clear. Amphetamines are excreted in breast milk in concentrations that may be higher than maternal plasma. In a study of a narcoleptic nursing mother who was treated with 20 mg daily of a racemic preparation of amphetamine, the concentration of amphetamine was three and seven times higher in breast milk than in maternal plasma on the 10th and 42nd day after birth, and small amounts of amphetamine were found in urine samples from the infant.[116] Whether breastfeeding should be discouraged in mothers who are unlikely to be adversely affected by erratic drug-seeking behavior is unclear and deserves further study.[117]

There are reports of infant restlessness and poor sleeping behavior after breastfeeding from amphetamine-exposed mothers, even though infant plasma levels are significantly lower than maternal plasma levels. Ilett *et al.*[118] examined the transfer of D-amphetamine to breast milk in four mother-infant dyads. Median daily dose was 18 mg per day (range 15 to 45). Median values for milk/plasma, absolute infant dose and relative infant dose were 3.3%, 21 $\mu g\,kg^{-1}$ per day and 5.7% of maternal dose, respectively. Plasma D-amphetamine was undetectable in one infant, and was present in the other two infants at concentrations that were approximately 6 and 14% of the corresponding maternal plasma concentration. Bartu *et al.*[119] showed that in the 24 h after a dose of methylamphetamines, average concentrations in milk were 111 and 281 $\mu g\,l^{-1}$ for methylamphetamines, and 4 and 15 $\mu g\,l^{-1}$ for amphetamine in two cases. Absolute infant doses for methylamphetamines plus amphetamines (as methylamphetamine equivalents) were 17.5 and 44.7 $\mu g\,kg^{-1}$ on day 1 for the two respective cases. From this, the authors suggest that breastfeeding should be withheld 48 h after a dose of amphetamines.

Furthermore, there are reports of adverse sequelae from breastfeeding after MA use, although none are substantiated by larger studies. Ariagno *et al.*[120] reported on a baby who died after breastfeeding from a MA-using mother. The concentration of MA in the infant's blood was 39 $\mu g\,l^{-1}$ and was put forward by prosecution as a cause of cardiopulmonary failure. This level was, however, 10 to 1000 times lower than adult doses, and the baby could have died of other causes, such as sudden infant death syndrome.

The long-term effects of prenatal amphetamine exposure

There is a well-deserved concern for the long-term outcomes of children exposed to prenatal amphetamines because of the neurotoxic properties of the drug. Human studies are, not surprisingly, confounded by a myriad of problems that may interfere with neurodevelopmental outcomes, such as poverty,[121] parental psychiatric co-morbidities[122] and parental chronic disease.[123]

Neurodevelopment

Brain imaging of MA users demonstrate structural and metabolic abnormalities, such as enlarged striatal volumes and reduced concentrations of the neuronal marker, N-acetylasparate and total creatine in the basal ganglia. There are reduced densities of dopamine, serotonin and vesicular monoamine transporters, and decreased dopamine D2 receptors, and altered limbic and orbitofrontal glucose metabolism that correlate well with the severity of psychiatric symptoms.[124] The effects of amphetamines on the developing, as opposed to the developed brain, are uncertain. Prenatal exposure to amphetamines may result in smaller striatal structures and elevated total creatine, but the clinical relevance of this is uncertain. Cloak *et al.*[125] showed

that prenatal MA exposure was associated with reduced apparent diffusion coefficient in frontal and parietal white matter, and higher fractional anisotropy in left frontal white matter, and suggest that prenatal MA exposure decreases myelination, increases dendritic or spine density and alters in white matter maturation.

Amphetamine-exposed newborn infants may demonstrate evidence of neurological stress, for example, poor quality movements, lethargy and hypotonicity.[58] In one of the largest follow-up studies of amphetamine-exposed children, Smith *et al*.[58] noted that there was little difference between the motor and cognitive outcomes of 4121 MA—exposed children at 3 years of age when compared with unexposed infants.

Contemporary studies of older amphetamine-exposed children are required. Subtle problems may have profound effects on educational achievement, and future employment and social prospects for the child. A Swedish study more than 15 years ago showed that amphetamine exposure resulted in poorer achievement in mathematics, Swedish language and sports.[126] Functional magnetic resonance imaging studies show decreased recruitment of the fronto-striatal circuit in 7 to 15-year-old MA-exposed children, when challenged with the visiospatial working memory 'N-Back' task.[127] Behavioral problems, especially aggression, may be a problem in the preteen years.[128] Animal studies suggest prenatal amphetamine exposure could lead to hypersensitivity to pain stimulation in the offspring[129] and adopted males,[130] and nociceptive disturbances may lead to long-term problems with behavioral responses and social adaptation.

Conclusion

Gestational amphetamine exposure is an increasing worldwide problem that may not always be easily identified during the neonatal period. This is of great concern, because amphetamines are neurotoxic and the abuse of these substances, even in so-called recreational users, is associated with lifestyle factors that may further impair the long-term cognitive and behavioral outcomes of exposed children. The long-term outcomes of amphetamine-exposed families are probably not a result of a simplistic linear relationship between drug exposure and outcome. More so than other drug-exposed families, these patients are more likely to be affected by complex psychosocial and environmental problems that may adversely affect outcome, even if drug exposure is minimal. A more robust and pragmatic screening tool, whether from detailed maternal history or toxicological assessment of new biological matrices like the umbilical cord, is urgently needed to identify exposed children and to implement intervention programs that may improve educational and behavioral outcomes. Certainly, newborn infants who are exposed only to amphetamines should not be evaluated against opiate-centric assessment tools, as this could lead to erroneous treatment of their condition. Further research into the assimilation of exposed children into society, the clinical evaluation of other problems, such as cardio-toxicity, and the need to develop more efficacious treatments for pregnant amphetamine-using women is an important gap in our drug-treatment service toolbox.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

JL OEI developed concept for article, prepared manuscript for submission. A Kingsbury, L Burns, J Feller, S Clews, J Falconer and M Abdel-Latif reviewed and revised the manuscript, and approved the final version for publication. A Dhawan assisted with the drafting of the manuscript.

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