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Methamphetamine Abuse During Pregnancy and its Effect on Fetal and Neonatal Outcome: A Review

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1. Abstract

The objective of this study is to summarize and review the literature data about Metamphetamines use during pregnancy, its effects on fetal and neonatal outcome. In the recent years the increase of metamphetamines abuser's women has become an emerging problem. Very little data has been published regarding the effects of prenatal metamphetamines exposure. We reviewed articles reporting the metamphetamines related toxicity both in the mothers and in the newborns. Amphetamines are neurostimulant and toxic drugs that became one of the most frequent and useful illicit substances. Studies on metamphetamines -exposed pregnancy outcomes have been limited because of many confounding factors such as other drug use, including alcohol, tobacco; poverty; poor diet, low social environment and lack of prenatal care. Abusing mothers are at high risk of psychiatric co-morbidity and obstetric complications that are often underdiagnosed due to poor symptoms. Real impact of metamphetamines abuse during pregnancy is not well know because the mothers did not consider that as a problem, also the withdrawal signs are less pronounced and they didn't participate to treatment programs. Data about short and long-term neonatal and child toxicity are lacking. Improve maternal and infant care are the goal in the next years to reduce the risk of serious toxicity in the perinatal period and improve their familiar long-term outcomes.

2. Introduction

Substance abuse during pregnancy has been recognized as a problem. All psychoactive drugs, including alcohol, tobacco and some prescribed medications, may have adverse effects on the pregnancy, the unborn child and the newborn. Different drugs, however, may act differently (Table 1). This effects may be a result not only of the drug itself, but also of poor overall health and the nutritional status of the drug-using mothers. Drug abuse can occur in all socioeconomic status but it is more frequent in people with low socioeconomic level, poor access to prenatal care, poverty, stress and psychological disorders. Due to the socioeconomic confounders as well as the presence of polidrug use in these subjects, it is often difficult to determine the real effect of a single substance in the mother, foetus and newborn.

Table 1: Health arms associated with substance use during pregnancy

	Alcool	Tobacco	Cannabis	Amphetamines	Cocaine	Opioids
Low birth weight	+	+	+	+		+
Miscarriage	+	+	+	+	+	
Perinatal mortality	+	+				+(+)
Developmental problems in childhood	+		+		+	
Foetal morbidity	+		+	+	+	
Premature birth	+			+		+
Decreased foetal growth	+					
Impaired intrauterine growth	+					+
Neonatal withdrawal symptoms	+					+
Premature rupture of membranes, placental abruption					+	
Preterm delivery	+					
Respiratory depression						+

(+) Related to withdrawal

The effects of these drugs may be confounded by polidrug use and/or other health and lifestyle associated with drug use

Source: A summary of health arms of drugs. The Centre of Public health, Faculty of Health and Applied Social Science, Liverpool John Moore's University (2011)

3. Drug Use and History

Methamphetamine (MTA) is the most widely consumed synthetic stimulant in the world and in many countries it is reported as the third most prevalent illicit drug after alcohol and cannabis [1]. Following its initial synthesis from ephedrine in Japan by Nagayoshi Nagai in 1893, MTA use has evolved over the years. Originally a non-controlled substance used as a medicine, it was then used as a stimulant by the military in World War II to enhance performance and increase concentration, and became known in Germany as "pilot's chocolate" and "pilot's salt". By the 1950s, the prevalence of amphetamine use increased among civilians and MTA abuse quickly became the cause of serious public health, social and security problems across the globe [2]. Today the problems associated with MTA use are especially visible in North America and Asia, and although MTA use remains limited in Europe as a whole, the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) found an increasing number of stimulant users, as well as increasing use of the injectable forms of these drug compared to previous years [3]. The prevalence of amphetamine use is a substantial global problem that affects almost all population's age groups. In 2018, an estimated 0.8 percent of young adults aged 18 to 25 were past year MTA users, 0.7% among adults aged 26 or older. Data from literature showed a decline in MTA use in young adults between 18-25 yrs old, but significant increases in adults >26 yrs old [4]. In the European countries, amphetamines are the third most prevalent drug, with 3.6 % reporting to have taken at some point in their life. Cannabis is by far the most used drug, with over a quarter using at some point during in lifetime, followed by cocaine, which reportedly 5% have used in their life. Among the age group in which drug use is highest, suggest that 1.2 million (1.0 %) young adults (aged 15–34) used amphetamines during the last year, with the most recent national prevalence estimates ranging from less than 0.1 % in Portugal to 3.6 % in the Netherlands [5]. The age group 2029 years had the highest share of the Dutch population who had taken amphetamines [5]. The legal use of these substances mostly regards the attention-deficit hyperactivity disorder (ADHD). It affects 7.5 million of children between the age of 2 and 17 in USA alone and more than 70% of these children have been prescribed amphetamines at least once. It has been suggested that also up to 5% of adults may have ADHD, including women of childbearing age who could require amphetamine treatment [6]. MTA was initially employed also for the treatment of obesity and narcolepsy. The clinical effect of MTA, resembling those of cocaine, are: increased alertness and attention, and decreased appetite and fatigue. Amphetamine-users become more alert, gain increased concentration, energy and sociability. Users need less sleep and food, but may also become irritable and aggressive developing wish of grandiosity and hallucinations. They are assumed orally, inhaled or injected. The clinical effects and toxicity of these agents are often indistinguishable from those of cocaine and the main difference is the longer duration of psychotropic action of MTA. (5-45 minutes' vs 2-12 hours). The appearance of a new smoked form of MTA ("ice") and the greater restrictions on the cocaine importation has made MTA the principal abused drug in several parts of USA. Amphetamine-users rapidly develop tolerance and dependence. Polydrug use, as benzodiazepines and alcohol, is a common problem in amphetamine-users and may greatly enhance the risk of adverse effects like overdose. Amphetamine users are highly unlikely to engage or stay in treatment programs, because they may not perceive their drug use as being problematic and they have a tendency to self-detoxify with both licit and illicit substances.

4. Pharmacology

MTA affects central nervous system (CNS) by releasing monoamine neurotransmitters such as dopamine, norepinephrine and serotonin, who are involved in the control of reward pathways in the mesolimbic and mesocortical system. MTA leads to many pharmacological effects due to its ability to use various molecular processes [7], such as increasing levels of monoamines by forcing the monoamines out of their storage vesicles and expelling them into the synaptic gap by making the dopamine transporters work in reverse [8]. Other mechanisms by which MTA are known to increase monoamine levels are by: 1) blocking the reuptake of monoamines by inhibiting the activity of monoamine transporters; 2) decreasing the expression of dopamine transporters at the cell surface; 3) increasing cytosolic levels of monoamines by inhibiting the activity of monoamine oxidase (MAO); 4) increasing the activity and expression of the dopamine-synthesizing enzyme tyrosine hydroxylase (TH). MTA has also a high lipid solubility that leads to a relatively fast transfer of the drug across the blood brain barrier. In addition, the production of nitric oxide, p53 activation resulting in apoptosis, excitotoxicity and mitochondrial damage may also be involved in the neurotoxicity of MTA. Futher, they may exert significant teratogenic effects on fetus through indirect mechanism, such as vasoconstriction resulting in fetal hypoxia and they could also act on the hypothalamus-pituitaryadrenal axis, disrupting fetal placental monoamine transporter expression and altering gene expression through epigenetic mechanisms, such as chromatin remodeling and DNA methylation. MTA are metabolized via cytochrome P450 2D6, which is absent in the human fetus until 22 weeks gestational age, leading to prolonged exposure of the fetus to high levels of MTA in utero [9]. The elimination half-life of MTA is dependent on the urine pH. When urine pH is six to eight, the half-life is about 12 hours, staying constant and unaffected by the route of administration [10].

5. Prenatal Effects

Very little data has been published regarding the effects of prenatal MTA exposure. Yet what is known about the effects of use during pregnancy is limited by studies using retrospective data on drug use with insufficient controlling for confounding factors, such as poverty, poor diet, lack of prenatal care and other drug and tobacco use. So, fetal amphetamine exposure has not, so far, been proven to be definitively teratogenic. In animal studies, the transplacental passage of MTA from pregnant ewes to fetus is rapid (<30s) and fetal drug levels gradually exceed maternal concentrations (>50%) due to reduced fetal metabolism and amphetamines and their metabolites are easily detectable in umbilical cord and placenta [11]. In pregnant rats MTA amniotic levels have been shown to correlate with brain amphetamine levels proving to be a valid indirect marker of cerebral exposure to the drug [12]. Data from literature demonstrated how amphetamines preferentially affect cardiac and neural cells. MTA administration to pregnant rat's results in abnormal cardiac development and myocardial damage reducing the number of beating cardiomyocytes and changing alpha- and beta-major histocompatibility complex in fetal and neonatal hearts [13], but further studies are needed to demonstrate cardiotoxicity in humans. A smaller head circumference in newborns exposed to MTA compared to those exposed to other drugs could be the result of a reduced dendritic length due to a depletion of serotonin, but no definitive structural abnormality in central nervous system has been definitively associated with amphetamine exposure [14]. The critical doses and the most sensitive period to the toxic effects of MA are not well known in humans. Rats exposed to MTA during prenatal day 12-22 and postnatal day 1-11 (approximately the second and third trimesters of human prenatal development) experienced significant behavioral deficits during development and in adulthood, suggesting that while MTA exposure in the early stages of pregnancy may not affect fetal brain development, exposure during later stages of prenatal or postnatal development (corresponding to neuroontogenesis) may be harmful. However further studies are needed to determine the critical period for MTA effects and refine the timing of drug discontinuation in pregnant women to minimizing the drug's impact in offspring [15]. Obstetric complications include a higher incidence of stillbirth, even associated with poor prenatal care, sexually transmitted diseases and cardiovascular accident as abruptio placenta and hemorrhage [5,8].Recently some different substances as methylenedioxymethamphetamine (NMDA) and methylenedioxyethamphetamine (MDEA) are diffused as recreational drugs. Their use during pregnancy have been reported, only in case series, with higher incidence of congenital defects, including limb anomalies and cardiac septal defects [16]. Others authors did not confirm this finding [17]. Use of NMDA together with MTA, vigorous exercise, poor diet and low social environment are considered as confounding factors in determine fetal effects.

Several European countries reported multidisciplinary comprehensive care programs. Doctors, psychologists and social workers follow up drug-using women and their children from early pregnancy into childhood to ensure the well-being and healthy development of the mother and the child. The Danish focal point reported that the occurrence of pregnancy and birth complications and birth defects among drug-using pregnant clients decreased considerably in the country as a result of comprehensive antenatal and postnatal care programs [18].

6. Neonatal Effects

Neonatal problem includes prematurity and IUGR, spontaneous abortion, stillbirth, cerebral infarctions and others vascular accident and neonatal neurobehavioral dysfunction. Fetal growth restriction, leading to smaller head circumference and lower birth weight, may result from the vasoconstrictive effects of norepinephrine as well as the diminished maternal nutrient supply secondary to the anorectic effect of amphetamine. Systemic effects

from altered noreprinephrme metabolism explain the transient alteration of cardiac rhythm as transient bradycardia or tachycardia reported in some prenatally exposed infants. Some studies report the association with cleft lip and palate in newborns exposed to MTA during early gestation (Pressinger 1998). Similar to adults, infants exposed to MTA present lethargy, somnolence and poor feeding. First trimester exposure resulted in greater total stress/abstinence and physiological stress, whereas third trimester and heavy use with increased lethargy and hypotonicity. Amphetamine-exposed infants may also present agitation and tachypnea, sometimes requiring gavage feeding and respiratory support and an increased risk of prolonged, but self-resolving, conjugated jaundice [19]. Interestingly, a case of unusually acute neurological and hepatic toxicity with symptoms mimicking the onset of severe perinatal asphyxia followed by acute cerebral hemorrhages, has been reported in a term- newborn exposed to MTA during pregnancy, but further studies are warranted to confirm this findings and to identify newborns at high risk of acute neonatal neurological MTA toxicity [20]. Table 2 show enhanced risk for various events after use of MTA compared with other drugs.

Table 2: Enhanced risk for various events or processes after substance use during pregnancy

Event or Process	Ethanol	Cigarettes	Cannabis	Opiates	Cocaine	Amphetamines	Barbiturates	Phencyclidine
Malformation	+	-	-	-	+	-	-	+
Abortion	-	+	?	?	+	+	-	+
IUGR	+	+	?	+	+	+	-	+
Prematurity	-	+	?	+	+	+	-	?
Withdrawal	?	-	-	+	-	-	-	-
Central nervous system sequele	+	?	?	?	+	?	-	?
Sudden infant death syndrome	+	+	?	+	+	?	-	?
Foster care	+	-	-	+	+	+	±	+

+ Cause event or process; - does not cause event or process? not known whether agent causes event or process; ± although risk is increased, the risk ratio range for many from 1 to 2 for these associations

7. Long Term Effects

Neurodevelopmental abnormalities have been described during the neonatal period and appear to persist until the adolescence as cognitive deficit, behavioral disturbances, hyperactivity, aggressiveness and sleep disorders [21]. Structural brain abnormalities have been also reported in prenatally exposed children. In magnetic resonance imaging (MRI) studies on children ranging from 3 to 16 years of age, exposed children scored lower on measures of visual motor integration, attention, verbal memory and long-term spatial memory. There were no differences among the groups in motor skills, short delay spatial memory, or measures of nonverbal intelligence. Neuroimaging demonstrated that prenatally exposed children had significant volume reductions in the putamen, globus pallidus, hippocampus and caudate [22] and showed as volume reduction in striatal and limbic structures were more severe in MTA exposed children than those with prenatal exposure to alcohol only, proving the high vulnerability of these brain structures to the teratogenic effects MTA. These reductions correlated interestingly with poorer sustained attention and delayed verbal memory [22]. Diffusion tensor imaging (DTI) suggests lower diffusion and higher fractional anisotropy in MTA exposed children at 3–4 years of age, indicating that fetal MTA may also alter white matter tracts [23]. Further, magnetic resonance spectroscopy (MRS) studies showed as exposed children had higher tCr, NA, and GLX in the frontal white matter (WM) and lower MI and MI/tCr ratio in the thalamus; these findings suggest higher neuronal density and cellular compactness in WM and lower glial content in thalamus, proving an aberrant neuronal and glial development in these brain regions [24]. Furthermore, lower MI in the thalamus seems to correlate with worse performance on a visual motor integration task [24]. Smith et al (2011) observed a lower fine motor performance at 1 year in exposed children, while at 3 years no differences were observed suggesting that MTA exposure has modest motor effects in the first year of life and they mostly resolved by 3 years of age [25]. The IDEAL study found a strong relation between prenatal methamphetamine exposure and rule-breaking and aggressive behavior. It also found a strong relation between adversities in the home and rule-breaking and aggressive behavior, proving that while prenatal MTA exposure is strongly related to behavioral and emotional control issues, early adversities may be a strong determinant of behavioral outcomes [26]. Interestingly data from animal studies, support the hypothesis that good maternal care can improve near and long-term functional changes in prenatally exposed animals and even though prenatal exposure to MTA triggered altered sensitivity to psychostimulants it not induce active drug-seeking. However, rats exposed to MTA in utero showed changes in the mesolimbic dopaminergic system and were more sensitive to the administration of an acute dose of MTA in adulthood, proving that offspring exposed to MTA in utero could be more sensitive to MTA and potentially to other psychostimulants [27]. MTA may affect fetal development via numerous mechanisms. Gut microbiota is a new research direction with great potential and value in underling mechanisms involved in intergenerational toxicity of prenatal MTA exposure. Numerous studies

have shown that maternal microbiota during pregnancy profoundly impacts offspring. We speculate that prenatal METH exposure and the consequences to offspring may be associate with gut microbiota. Synergy between environmental susceptibility during pregnancy and METH exacerbates the risk of neurodevelopmental disorders [28].

Some studies reported that long term effects have been associated with the extent and the duration of prenatal exposure to MTA and with the severity of head growth restriction during pregnancy [29]. Swedish data revealed striking gender differences in children exposed, boys were taller and heavier, girls smaller and lighters. This finding suggests that MTA prenatal exposure interfere with puberty, accelerating it in boys and delaying in girls, probably influencing the neurodevelopment of adenohypophysis [30]. During adolescence young patients born by an abusing mother developed also social problem including abandonment, abuse and neglect. In Sweden only 22% of these children remain on the care of their mothers, whereas 70% of them were in foster care.

Moreover, impact of prenatal MTA exposure on long term neurodevelopment is an ongoing debate. Authors reported that, based on currently available evidence, prenatal methamphetamine exposure has transient effects on gross motor development, no effect on language and cognition, and modest effects on behavior and executive functioning with poor inhibitory control, which may be attributable to early adversity [31].

8. Diagnosis and Management

Detection of amphetamine exposure in newborn depends on the timing of last maternal ingestion. Accurate identification of drug-exposed newborns relies on maternal history, clinical presentation of the newborn and laboratory testing of biological maternal matrices (ie: urine, blood, oral fluid, sweat, hair, and breast milk), neonatal matrices (ie: urine, meconium, hair, and umbilical cord blood and tissue), and/or matrices from both the mother and neonate (ie: placenta and amniotic fluid). Evaluation of these sample can account for in utero exposure at various stages of gestation and approximate the period (recent vs chronic use) of substance exposure. Each matrix has its own unique advantages and limitations in terms of ease of collection, the window of gestational exposure represented, and sensitivity for different parent drug analytes and metabolites, and Neither neonatal urine nor meconium (the first neonatal stool), the two most commonnewborn matrices used for drug testing, are able to detect early gestational drug exposure. Meconium provides a valid picture of maternal drug use from the 16th week of gestation, but false-positive results may be high (> 40%) and obtaining the minimum sample of dried meconium required for standard panels of drug tests may be difficult, even with serial collections of stools. The second most common matrix used for drug testing are neonatal urine, but even in cases of prolonged exposure, MTA metabolites may be detectable only in the first 23 days of life due to their short half-life (i.e., 16 to 31 h) and maternal labetalolo may also create falsepositives [32]. Other biological matrices that show diagnostic promise are hair, nails, amniotic fluid, the placenta and the umbilical cord, but the use of these matrices is limited by technical and practical feasibility.

9. Breastfeeding

Breastfeeding in women using drugs requires careful consideration. MTA passes freely into breast milk and the Academy of Breastfeeding Medicine state that women who have used substances in the previous 30 days should not breastfeed [33], particularly if they have positive urine drug screens and have not engaged with pregnancy services or alcohol and drug treatment services. Indeed, little data exist about breastfeeding and illicit drugs, and not all addicted women have the same pattern of MTA use (intravenous, smoked, orally), so advice about breastfeeding will vary. Pregnancy and motherhood are powerful motivators to stop or reduce substance use and for women who are occasional MTA users, pregnancy provides sufficient reason for abstinence, while for substancedependent women, this is more difficult [34]. Early engagement in antenatal care and in substance use intervention increase chances of MTA abstinence and lifestyle improvement. Regular multidisciplinary team care in a nonjudgmental environment facilitated mother engagement in antenatal and neonatal care. Women's interest in breastfeeding and wanting to do the best for their infant should be good motivators to address substance use, but since complete abstinence is rare and brief substance use episodes are common, a breastfeeding safety plan is essential [35]. Bartu et al. showed that in the 24 h after a dose of intravenous methylamphetamines, average concentrations in milk were 111mcg/L and 281 mcg/l l in two nursing mother and the absolute infant doses were 17.5 and 44.7 mg/kg/die [36]. Similarly, for 4 women who took a range of 15 to 45 mg of dexamphetamine, the average absolute infant dose was 21 (11-39) μg/kg/day and for a woman who took 20 mg of oral amphetamine daily, the absolute infant dose was 10 μg/kg/ day [37]. These estimated mg/kg infant doses of methamphetamine are lower than therapeutic doses of the equipotent dextroamphetamine for older children with attention deficit hyperactivity disorder. However, this is not evidence of safety for breastfed infants because data on these women cannot be extrapolated to other methamphetamine abusers. Ariagno et al reported the case of a two-month-old infant who died after nasal inhalation methamphetamine dose by his mother, but low serum methamphetamine levels (39 mcg/L) did not definitively justify infant's death [38].

However, clinicians must evaluate the risks and benefits of breastfeeding on a case-by-case basis. For ongoing MTA use, breastfeeding should not occur, at least up to 48-100 hours after the last MTA dose, although in many mothers methamphetamine become undetectable in breastmilk after an average of 72 hours from the last use [34]. Breast milk is negative up to 1 day prior to the mo-

ther's urine becoming negative, so a negative maternal urine test can be a valid marker for safety initiating breastfeeding [39-41]. However, even urine drug screen may assist clinical decisions, the entire clinical picture should be considerate. Depending on the assay, urine test for amphetamines may be positive for 2–5 days after use, but false positives secondary to prescription drugs (e.g., antidepressants, H2 receptor antagonists such as ranitidine) may occur [42] and sometimes drug screens may cause some women to disengage from care [43,44]. Thus, postpartum management of these women is wrought with dilemma, from withholding breastfeeding for fear of exposing the infant to MA to initiating early breastfeeding in the hopes of increasing mother–infant bonding and a sense of well-being, which, in turn, might keep the mother drug-free after discharge. In conclusion, the recommendation to initiate breastfeeding after a negative urine MTA results are, at best, optimistic. Most women will continue to abuse MA at home, and without an active surveillance system, the absolute infant dose will no doubt increase significantly and the safety of continued breastfeeding will once again become a true concern.

10. Conclusion

MTA abuse during pregnancy is an increasing worldwide problem that may not always be easily identified during the neonatal period. Fetal and perinatal exposure are associated with an unfavorable neonatal effects and impaired long-term cognitive and behavioral outcomes.

Pregnant women who abuse MTA are more likely to be affected by complex psychosocial and environmental problems and regular multidisciplinary team could facilitate mother engagement in antenatal and neonatal care. MTA toxicity are well known in animal models, but as polydrug use is common among pregnant women who abuse recreational substances further studies may be helpful to understanding the near- and long-term effects in humans of methamphetamine-only abuse during pregnancy.

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