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Stimulant Use in Pregnancy – an under-recognized epidemic among pregnant women

Marcela C. SMID, M.D. M.A. M.S.[1,2,3], **Torri D. Metz, M.D. M.S.**[1], and **Adam J. Gordon, M.D. M.P.H.**[2,3]

[1]Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, University of Utah School of Medicine, Salt Lake City, UT

[2]Program for Addiction Research, Clinical Care, Knowledge and Advocacy (PARCKA), Division of Epidemiology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City UT

[3]Informatics, Decision-Enhancement, and Analytic Sciences Center (IDEAS), Salt Lake City VA Health Care System, Salt Lake City, Utah, USA

Abstract

Stimulant use, including cocaine, methamphetamines, ecstasy, and prescription stimulants, in pregnancy is increasingly common. In the US, stimulants are the second most widely used and abused substances during pregnancy and pregnant women using stimulants in pregnancy are at increased risk of adverse perinatal, neonatal, and childhood outcomes. In this review, we describe the pharmacology, pathophysiology and epidemiology of stimulants, summarize the maternal and neonatal effects of perinatal stimulant use, and outline treatment options for stimulant use disorders among pregnant women. Development of effective treatment strategies for stimulant use disorders identified among pregnant women are urgently needed.

Keywords

pregnancy; substance use disorder; methamphetamine; cocaine; bath salts; ecstasy

Introduction

Stimulants, including cocaine, ecstasy, methamphetamines and prescription stimulants, are the second most widely used and abused substances in the United States.[1] The lifetime prevalence among adults for stimulant use is 29.2%, second only to marijuana 46.9%.[1] Also known as “uppers,” stimulants refer to any drug that increases activity of the central nervous system or those with sympathomimetic properties. Stimulants are widely used both for medical purposes including mood disorders, impulse control disorders such as attention deficit disorder, sleep disorders and obesity.[2–5] Because of their euphoric effects, they can be

CORRESPONDING AUTHOR: Marcela Smid, M.D. M.A. M.S., 30 N 1900 E #2B200 Salt Lake City, UT 84132 USA Tel: (801) 587-9941; Fax: (801) 585-2594, Marcela.Smid@hsc.utah.edu.

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used illegally for recreational and performance-enhancing purposes. While the rate of stimulant use is similar between men and women, it is increasingly recognized that women may be disproportionately vulnerable to developing stimulant misuse and abuse due to factors related to hormones[6–9] and reinforcement of gender constructs.[10–12] Women progress faster from first exposure to addiction than men—known as telescoping—presenting additional challenges to preventing stimulant use disorders.[13,14]

In 2015, 1.38 million reproductive age (15–44 years old) women used a stimulant in past month (misuse of stimulant prescriptions 1.0%; cocaine 0.7%; methamphetamine 0.7%; ecstasy 0.3%).[1] In the US, stimulant use among pregnant women has increased consistent with the nationwide rise in use rates. Stimulant use among pregnant women is of growing public health concern and is associated with several factors including psychiatric co-morbidities,[15,16] poverty and social isolation,[17,18] history of trauma[19] and domestic violence,[20,21] all of which impact maternal and child health outcomes. In the 21st century, attention has shifted to the impact of the opioid epidemic on pregnant women;[22] however, prenatal stimulant use is more common than opioid use.[23,24]

The purpose of this article is to describe the pharmacology, pathophysiology and epidemiology of stimulants (cocaine, methamphetamine, prescription stimulant misuse, ecstasy, ephedra and bath salts), summarize the maternal and neonatal effects of perinatal stimulant use and outline treatment options for stimulant use disorders among pregnant women.

Cocaine

Pharmacology, pathophysiology and epidemiology—Cocaine is derived from the coca bush *Erythroxylon coca*, which is native to the Andes Mountain of South America. It produces a dramatic prolonged adrenergic stimulation by presynaptic uptake of sympathomimetic neurotransmitters (norepinephrine, serotonin and dopamine).[25,26] The psychoactive effects of cocaine derive from the prolonged effect of dopamine on the brain's limbic system and cerebral cortex. Cocaine is used in three primary preparations: 1) base ("crack cocaine") which has a low melting point and when heated, vaporizes allowing it to be smoked and 2) hydrochloride salt which has a high melting point, thus cannot be smoked because it is destroyed by heat, but is water soluble making it easier to dissolve for injection and intranasal use. While crack cocaine possession is associated with higher legal penalties, cocaine base and hydrochloride salt have identical physiological and psychological effects on the mother and fetus. Cocaine rapidly crosses the maternal and fetal blood brain barrier and the placenta by simple diffusion, causing generalized vasoconstriction by directly affecting fetal and maternal blood vessels.[27] Vasoconstriction of maternal vessels has indirect effects on the fetus, which may lead to utero-placental insufficiency, acidosis and fetal hypoxia.[28]

In the 1980's and 1990's, rising cocaine use, particularly in urban and minority communities, and the emergence of the "crack baby" phenomenon ultimately led to the stigmatization of pregnant women with substance use disorders.[29] In the general population, 40% of emergency department visits related to substance use are associated with cocaine, making it the leading cause of illicit drug use associated visits.[30] Among women who also

use opioids for non-medical purposes, 9.4% of reproductive age women (18–44 years) used cocaine in the past 30 days and 7.4% used methamphetamine or other stimulants.[31] In 2015, cocaine was the second most common illicit substance used by pregnant women; 3.4% of pregnant women used cocaine in the past month.[1] Pregnant women using cocaine or crack cocaine tend to be older, African-American and of low socioeconomic status.[32,33] While on the decline, cocaine abuse remains the leading cause of antepartum hospitalizations for substance use among pregnant women.[34]

Cocaine and perinatal outcomes—Maternal complications of cocaine use in pregnancy include cardiovascular complications such as hypertension, myocardial infarction and ischemia, renal failure, hepatic rupture, cerebral ischemia/infarction and maternal death.[35–41] Cardiovascular complications of cocaine are not dose-dependent and small doses may lead to cardiac morbidity and mortality in otherwise healthy pregnant women.[42] Pregnancy may increase the cardiovascular toxicity of cocaine due to cardiac muscle's sensitivity to cocaine in the presence of increasing progesterone concentrations.[43–45] Contractility of papillary muscles of pregnant and non-pregnant progesterone-treated female rats becomes severely compromised at substantially lower cocaine concentrations compared to non-pregnant female rats.[46] At the time of cesarean, active cocaine use may lead to combative behavior, cocaine-induced thrombocytopenia, ephedrine-resistant hypotension, and altered pain perception due to altered μ and κ receptors despite adequate pain levels.[47] Among pregnant women, cocaine toxicity may cause severe hypertension, hyperreflexia, proteinuria, edema and seizures, which can be easily confused with preeclampsia.[39,48] Beta-adrenergic antagonists, including labetalol and propranolol, should be avoided as they may create unopposed alpha-adrenergic stimulation and are associated with coronary vasoconstriction and end-organ ischemia.[47] In the case of suspected maternal cocaine toxicity, hydralazine should be used for the treatment of hypertension.[42]

Since the 1980's, hundreds of peer-reviewed articles have been published linking maternal cocaine use to adverse pregnancy outcomes. However, many of these studies do not control for important confounders including maternal age, poverty, stress, co-occurring psychiatric comorbidities, other substances including tobacco, alcohol and other drugs. There is disagreement on whether cocaine use increases the risk of structural malformations,[49] although some studies show an increase in urinary tract anomalies,[50–52] and other studies show an increase in vascular disruption-type abnormalities, including limb reduction and intestinal atresia.[53]

Gouin et al (2011)'s systematic review and meta-analysis of 31 studies found that cocaine use puts women at increased risk for five adverse perinatal outcomes: preterm delivery, low birth weight (< 2500 gms), small for gestational age infants, earlier gestational age at delivery and reduced birth weight.[54] Maternal cocaine use is also associated with increased risk of vertical transmission of HIV, hepatitis and syphilis.[49] Several authors have noted that some women report that cocaine use is associated with shorter labor duration; however, studies suggest that while labor duration appears to be similar, women do present with more advanced cervical dilatation and at an earlier gestational age than women who do not use cocaine.[55,56] Some studies also suggest increased risk of miscarriage,[57] stillbirth,[58] placental abruption[59,60] and uterine rupture.[61] In a meta-analysis, after controlling for other factors,

increased risk of sudden infant death syndrome could not be associated with cocaine use alone.[62]

Cocaine is found in breastmilk[63] and active illicit drug use, including cocaine use, is considered a contraindication to breastfeeding.[64,65]

Cocaine use and long-term maternal and childhood outcomes—Very little is known about postpartum outcomes among mothers with prenatal cocaine use. Postpartum psychological distress was greater among mothers with prenatal cocaine use compared to mothers not using cocaine.[66] Definitive studies of long-term outcomes among children with cocaine exposure remain elusive. Some studies have found that children with prenatal exposure have dysregulated behavior,[33,67] growth,[68] inhibitory control,[69] attention[70] and abstract reasoning.[68] In a systematic review of 36 studies of children younger than six years of age assessing physical growth, cognition, language skills, motor skills, attention, affect and neurophysiology, Frank et al. did not find compelling evidence that prenatal cocaine exposure is associated with adverse outcomes that cannot be attributed to gestational age at delivery, caregiver psychiatric co-morbidities, other prenatal exposures (tobacco, marijuana or alcohol) or quality of postnatal environment.[71]

Methamphetamines

Pharmacology, pathophysiology and epidemiology—Methamphetamine, also known as speed, ice, crank and crystal meth, is the methylated derivative of dextroamphetamine. Methamphetamine is a central nervous system stimulant and causes the presynaptic concentration of dopamine, serotonin and norepinephrine. Its use is associated with intense euphoria and energy. It is the only illicit substance that can be manufactured from commonly available items such as over-the-counter cough syrups and decongestants.[72] It can be snorted, smoked, used rectally and injected with high bioavailability.[72,73] Because of its alpha and beta adrenergic properties, methamphetamine increases the risk of myocardial infarction, hypertension, cardiomyopathy and stroke.[72] Illicit use of methamphetamine has been strongly linked with severe dental disease[74] and increased risk of infection including HIV and Hepatitis C.[75,76]

Methamphetamine use has escalated in the past two decades and represents a serious public health concern among reproductive age women. From 2010–2014, the rate of drug overdose involving methamphetamine has doubled.[77] In 2015, 1.7 million individuals (0.6% of the population) used methamphetamine in the past year; of those, 52.7% used in the past month.[1] From 2005 to 2015 among persons who inject drugs, the proportion reporting injecting methamphetamine increased from 2 to nearly 30%.[78] Compared to men, women have lower lifetime (6.6 vs 4.1%), past year (0.9 vs 0.4%) and past month use (0.5 vs 0.2%) use of methamphetamines.[1] Women who use methamphetamines are at substantially increased risk of death; they have an observed death rate 26 times that of women who do not use.[79] In contrast, men who use methamphetamines have an observed death rate six times higher than men who did not use. Among high school students (9^{th} to 12^{th} grade), lifetime use of methamphetamine is 6.8% and is a significant risk factor for adolescent pregnancy.[80]

Among pregnant women, methamphetamine use has also increased. From 1988 to 2004, hospitalization for amphetamine abuse among pregnant women doubled while cocaine abuse decreased 44%.[34] During the same time period, nearly a quarter million pregnant women were admitted to federally funded treatment centers in the United States for methamphetamine treatment, making it the primary substance for which pregnant women seek care. [24]

Pregnant women using methamphetamine are more likely be white (64%), unemployed, and less than 24 years old.[24,34] They are also more likely to have significant psychiatric disorders,[15,81] live in poverty, and have lower perceptions of quality of life. They are also at increased risk for legal complications and have a greater likelihood of substance use among friends and family than those not using.[82]

Methamphetamine and perinatal outcomes—While methamphetamine use among pregnant women is associated with adverse perinatal outcomes including fetal death,[83] growth restriction[84] and preterm birth,[15] most studies are unable to distinguish between methamphetamine exposure and other factors including maternal co-morbidities, other drugs, smoking, contaminant in non-pharmaceutical preparation or poverty.[16,85–88] In a single center study, women using methamphetamine in pregnancy were more likely to have a preterm delivery, cesarean delivery, neonatal death and maternal intensive care unit admission. However, this study did not control for other factors including smoking, other drug use or socioeconomic status.[88] In a meta-analysis of eight studies, methamphetamine use during pregnancy was associated with earlier gestational age at delivery, lowler birthweight and smaller head circumference.[89] There was no difference in preeclampsia or other hypertensive disorders of pregnancy in this meta-analysis. However, in a study comparing women who were hospitalized for cocaine and methamphetamine in pregnancy, infant morbidity including premature delivery and poor fetal growth were more common in the cocaine using group, whereas vasoconstrictive effects such as cardiovascular disorders and hypertension complicating pregnancy were more common in the amphetamine using group.[34]

Several case reports and retrospective studies have suggested increased risk of congenital anomalies with methamphetamine use including cardiac defects,[90,91] gastroschisis,[92] limb reduction,[93] biliary atresia[94] and neural tube defects.[95] However, several prospective studies have failed to demonstrate an association between methamphetamine use and anomalies with the exception of cleft palate.[15,96,97] Infants with prenatal exposure to methamphetamines may develop a constellation of symptoms including jitteriness, drowsiness and respiratory distress suggesting amphetamine withdrawal, although very few will require pharmacological intervention [98,99]

Methamphatemine is neurotoxic,[100,101] making prenatal exposure particularly concerning for fetal brain development. In animal models, maternal use of methamphetamines resulted in preferential concentration of metabolites in the fetal brain.[102] Effects on the fetal brain were gestational age dependent; exposure to methamphetamine in early to mid trimester produced long-lasting effects on the serotonergic development of the fetal brain.[103] Sex differences in methamphetamine exposure may start in the fetal period. Male offspring with

prenatal exposure to methamphetamine may be at increased risk of drug-induced neurotoxicity as adults.[104] There is a paucity of neuroimaging studies of children exposed to methamphetamine prenatally. In two studies using the same population, smaller subcortical brain volumes and alterations in cellular metabolism in the basal ganglia were noted among methamphetamine-exposed children versus unexposed children.[105,106] Notable limitations of these studies include more alcohol and tobacco exposure in the methamphetamine group compared to the control group.

Methamphetamine use and long-term maternal and child outcomes—Similar to cocaine, long-term studies of children exposed to methamphetamine are limited. However, the Infant Development, Environment and Lifestyle study (IDEAL) has followed 412 maternal-child pairs (204 methamphetamine exposed versus 208 unexposed pairs) from the United States and New Zealand longitudinally from delivery through childhood providing valuable insight into maternal postpartum outcomes and infant and child development.[82,99,107,108] Infants were matched with controls based on prenatal exposure to alcohol, tobacco, marijuana and maternal depression. Infants exposed to opioids and cocaine were excluded, limiting the generalizability of study findings. At one month of age, one-third of women with prenatal methamphetamine use did not have custody of their children compared to 2% of women with no use.[82] Prenatal methamphetamine exposure has been linked to increased likelihood of admission to the neonatal intensive care unit, decreased arousal and increased physiological stress[81,108,109] which subsequently improved at one month of age.[110] Mothers with prenatal methamphetamine use were also more likely to be depressed which correlated with poorer infant autonomic stress response.[111] At age three, differences in cognitive, behavioral, language and emotional outcomes between exposed and unexposed children were correlated with adverse social environments and not prenatal methamphetamine exposure.[112] However, in subsequent studies of the same IDEAL population, heavy prenatal methamphetamine exposure (≥ 3 days per week) was associated with anxiety/depression and attention problems by age 3 and 5 years after controlling for other substances and caregiver/environmental risk factors.[113,114] In the IDEAL cohort, children exposed to methamphetamine at age 7.5 years had poorer cognitive function on the Conner's Parent Rating Scale, but not behavioral problems.[115]

Several neuroimaging and cognitive function studies have assessed structural brain development of children with prenatal methamphetamine exposure. In a study of children aged 3–4, there were no differences in global cognitive functioning between methamphetamine exposed versus control groups.[116] Methamphetamine exposed children did perform worse on visual motor processing tests than control children; however, a large number of tests were performed without adjustment for multiple comparisons.[116] While not correlated with functional differences, methamphetamine-exposed female children had changes in frontal white matter suggestive of altered neuronal and glial development. Several studies using neuroimaging to assess structural brain development of children 7–15 years old with prenatal methamphetamine exposure have demonstrated alterations in the striatum and frontal lobes with sex differences, suggesting that prenatal methamphetamine exposure leads to 1) rewiring of corticostriatal networks, 2) a differential effect in male and

female children, 3) changes that persist into late childhood and adolescence and 4) structural differences that are correlated with cognitive and functional differences.[117–121]

Methamphetamines are excreted in the breastmilk[122] and, as with cocaine, active illicit drug use is a contraindication to breastfeeding.[64,65]

Prescription stimulant misuse

Prescription stimulants including a mixture of amphetamine salts (Adderall), lisdexamfetamine (Viviane) and methylphenidate (Ritalin) are primarily used for the treatment of attention deficit and hyperactivity disorder (ADHD), which affect 3–7% of young people. Among college students, the life-time prevalence of non-medical prescription stimulant use was 6.9–8.1%, past year prevalence was 4.1–5.4% and past month prevalence was 2.1%.[123,124] Non-prescription use of stimulants includes those taking medications not prescribed to the individual or not taking as directed (exceeding quantity, alternative routes such as intranasal). Among reproductive age women, 3% of women have ADHD and in cases of moderate to severe impairment, the benefits of prescription stimulant use may outweigh risks.[125] In 2015, 1% of reproductive age women reported prescription stimulant misuse.[1]

Prescription misuse effect on pregnancy—Very little is known about prescription misuse of stimulants. Most known data about prescription stimulant use are derived from studies of women treated for ADHD during pregnancy. Based on several population-based cohort studies, first trimester exposure to prescription stimulants does not appear to be associated with increased risk of congenital anomalies.[126–128] Among women taking prescription stimulant medications, there was a small increased risk of preeclampsia and preterm birth.[129] Among women who filled at least two prescriptions for stimulants between 8 and 18 weeks, the risk of placental abruption increased. Those continuing to the third trimester had an increased risk of preterm delivery. Women in this cohort were receiving prescriptions from medical providers and the proportion of women misusing these medications is unknown.

Among women treated primarily with methylphenidate during pregnancy, there was an increased risk of neonatal seizures and NICU admission in one population-based Swedish cohort study. However, authors acknowledge residual confounding which limits the ability to directly attribute these findings to stimulant use.[130] In another Australian study of women with ADHD, treatment with stimulants both before and during pregnancy was associated with adverse outcomes, including preeclampsia and preterm birth, at similar rates, suggesting that stimulant treatment did not account for the increased risk.[131] Notably, both of these studies assume that pregnant women take medications as prescribed and markers of misuse (early refills, multiple providers, multiple pharmacies) were not assessed.

Amphetamines are excreted in human breastmilk, however very limited data are available. A threshold of 20 mg daily is suggested as quantity sufficient to detect metabolites in the neonatal urine, however, this is based on the study of one woman treated for narcolepsy with amphetamine 20 mg daily followed for six weeks pospartum.[132] Despite known passage into the breastmilk, no adverse neonatal effects were identified in a cohort of 103 breastfed

infants with prescription amphetamine exposure.[133] While illicit stimulant use, including prescription stimulant misuse is a contraindication to breastfeeding,[64,65] use of prescribed stimulants as directed may not be associated with increased risk.

Ecstasy (N-methyl-3,4-methylenedioxyamphetamine; 3,4-methylene-dioxymethamphetamine)

N-methyl-3,4-methylenedioxyamphetamine; 3,4-methylene-dioxymethamphetamine (MDMA), commonly referred to as Ecstasy, E and Molly, is an amphetamine used for recreational purposes. An estimated 6.4 million people have used MDMA[1] and exposure among high school age children has dramatically increased.[134] In 2015, 0.3% of reproductive age women used MDMA in the past year.[1] Pregnant women who use MDMA during pregnancy are more likely to suffer negative consequences including work and social problems compared to those who did not use MDMA.[135]

MDMA effects on pregnancy—There is limited information on effects of MDMA in pregnancy. In the largest prospective study, 71 women had MDMA only exposure and 56 women had MDMA and other substance exposure. Of continued pregnancies (n=78), 15.4% of infants had congenital anomalies, which is higher than the expected frequency (2–3%).[134] Cardiovascular (26 per 100 livebirths versus expected 5–10 per 100) and musculoskeletal malformations (38 per 100 livebirths versus expected 1 per 1000) were most common. There is one additional case report of a congenital heart defect with prenatal MDMA exposure.[136] A case-control study found that MDMA exposure was associated with vasoconstrictive disorders including gastroschisis; however, there were only seven women with prenatal exposure in this cohort.[92] There is little known about other pregnancy outcomes or lactation with MDMA.

MDMA and long term maternal and child outcomes—Like methamphetamine, MDMA is neurotoxic.[137] Little data are available on maternal outcomes after MDMA prenatal use. Several studies have suggested that MDMA is associated with worse infant outcomes, including poorer motor quality and lower milestone attainment, in a dose dependent fashion.[135,138] The observed developmental delays particularly in fine and gross motor delays persisted at 24 months.[139,140]

Ephedra

Ephedra, found in several *Ephedraceae* species, is a commonly used herb in Chinese and Western herbal traditions. In Chinese traditional medicine, it is also known as ma huang. Ephedra contains ephedrine, pseudoephedrine, norephedrine and norpseudoephedrine. At high doses, ephedra use has been associated with cardiovascular complications and death in the general population.[141,142] Among individuals with co-existing psychiatric disorders or in the presence of polysubstance use, ephedra has been associated with psychosis, severe depression, mania and suicidal ideation.[143] Among US adults, 3.9% report using ephedra (ma huang).[144] Ephedra is reportedly one of the more commonly used herbs with 1.1% of women reporting use three months prior to pregnancy and 0.6% in the first trimester.[145] In one study of women using weight loss products, approximately 1% of women reported using ephedra-containing products inadvertently in the peri-conception period. In the National

Birth Defects Prevention Study which included 18438 women from 10 states from 199–2003, 1.3% reported using ephedra during pregnancy.[146] There were five cases of anencephaly among women with ephedra use, however, there was no statistically significant association compared to women no using ephedra (odds ratio 2.8, confidence interval 1.0–7.3). Very little is known about ephedra use and perinatal outcomes or lactation.

Natural and Synthetic Cathinones

Natural and synthetic cathinones contain simulants derived from the khat plant (Catha edulis) which is native to East Africa and the Arabian Peninsula. Khat leaves contain two stimulants cathinone and methcanthinones and are chewed for mild stimulant properties. Synthetic cathinone, widely known as “bath salts,” are considered part of a group of “new psychoactive substances” that unregulated psychoactive substances with no legitimate medical use.[147] They are introduced and then reintroduced in quick succession to obstruct law enforcement. Synthetic cathinones are generally white or brown crystal-like powder and can produce increased friendliness and sex drive, agitation, violent behavior and hallucinations. They are illegal in most states due to adverse mental and physical effects.[148,149] The three most popular bath salt constituents include mephedrone, methylone and 3,4-methylenedioxypyrovalerone (MDPV). Cathinones act at the dopamine, serotonin and norepinephrine synapses and produce stimulant similar effects to methamphetamines and cocaine.[150] One study found that MDPV is ten times more potent than cocaine at producing locomotor activation, tachycardia and hypertension in rats.[151] MDPV has been implicated in bath salt overdoses in the United States and produces a cocaine-like blockage of transporters for dopamine and norepinephrine. Because of action at the serotonin transporter, bath salt overdose is associated with serotonin syndrome which manifests as agitation, psychosis, hyperthermia and tachycardia.

The epidemiology of bath salt use is limited. Among high school seniors, 1.1% have used bath salts in the past year.[152] In an on-line survey of predominantly educated white males, (N=113), bath salt use was associated with increased sexual desire and high risk sexual behaviors.[153] To our knowledge, there is no available information on the prevalence of bath salt use among reproductive age or pregnant women.

Cathinones and perinatal outcomes pregnancy—Studies from Africa and Middle East demonstrate an association between khat use and decreased uterine blood flow and decrease in birth weight.[154–156] A small study (N=642) in Yemen found no increased risk of stillbirth or congenital malformations among pregnant women who chewed khat during their pregnancies.[157] Among lactating women who chew khat, nor-pseudoephedrine has been found in breast milk.[158] In a study of women who chewed khat while breastfeeding, 75% women who chewed khat four or more times a week had a history of a child dying compared to 7% of women who chewed khat once a week; however the study did not account for other significant confounders of childhood mortality in this region, including age of children, socioeconomic status and amount of breastfeeding.[159] There are no studies currently available on the maternal, fetal or childhood effects of bath salts.

Treatment of stimulant use disorders among pregnant women

There is no Food and Drug Administration (FDA) approved pharmacotherapy for stimulant use disorder. In the non-pregnant population, studies of pharmacotherapy for cocaine and amphetamine use disorders have largely shown no efficacy for any pharmacotherapy including anti-depressants, anti-convulsants and dopamine agonists inhibitors.[160] Psychosocial treatments appear to be the only effective treatment for stimulant use disorders.[161] Most notably, contingency management, also known as motivational incentives, provides rewards for desired behaviors (i.e. negative drug test) and withholding privileges for undesired behaviors (i.e. relapse) appears to be most effective for treatment of stimulant use disorders.[162]

However, studies often exclude reproductive age women due to fears of unintentional effects on the fetus in the event of unanticipated pregnancy. The growing body of evidence that stimulant use has important gender and sex differences suggests that studies on effective treatment of reproductive age and pregnant women are urgently needed. Clinicians and policymakers should be aware of the impact of stimulant use during pregnancy and significant resources are needed to adequately to address this epidemic.

Conclusions—Stimulant use in pregnancy is an under-recognized public health epidemic and has important short-term and long-term implications for maternal and neonatal health (Table 1). Illicit stimulant use is likely associated with adverse perinatal outcomes including shorter gestational age and low birth weight, however, less is known about prescribed stimulant use and perinatal outcomes. Little is known about safety of stimulant use during breastfeeding. Screening for substance use, including prescription use for non-medical purposes and illicit stimulant use, is recommended by the American College of Obstetricians and Gynecologist and the American Society for Addiction Medicine.[65] Despite these recommendations, the majority of obstetrical providers do not systematically screen pregnant or postpartum women for substance use and are likely to miss women using stimulants if selective screening is based on age, race/ethnicity or socioeconomic status.[163,164] Post-partum screening may be particularly important as risk of drug relapse is highest in the postpartum period.[165,166] Among women identified at low or moderate risk may respond well to brief intervention, however, those at high risk of a stimulant use disorder likely need referral to treatment.[163] Significant research gaps exist regarding stimulant use disorders among pregnant and postpartum women (Table 2). Research studies have systematically excluded pregnant and lactating women from studies on pharmacological therapy for stimulant use disorder despite a growth body of literature showing important sex and gender differences in treatment responses. Systems barriers for pregnant and postpartum women also prevent many women from seeking treatment for stimulant use disorder. In general, many drug treatment programs do not admit pregnant women or parenting women with children. Once they delivered, many women face loss of insurance after pregnancy which may disrupt or preclude substance use treatment. Pregnancy and family-oriented treatment approaches are urgently needed. Furthermore, research studies on novel treatment approaches for stimulant use disorder should systematically *include* pregnant and postpartum women given the association between adverse perinatal outcomes and untreated stimulant use disorder. Finally, long-term studies that track family based outcomes are

needed to understand the interplay of maternal, paternal and childhood outcomes associated with perinatal stimulant use.

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Table 1:

Maternal, perinatal, fetal and childhood outcomes associated with stimulant use

Substance	Maternal effects	Perinatal effects	Structural fetal anomalies	Childhood neurodevelopmental effects
Cocaine	Cardiovascular complications including: • Hypertension • Myocardial ischemia and infarction • Cardiotoxicity Infectious disease (HIV, Hepatitis B and C) Renal failure Hepatic rupture Thrombocytopenia Cerebral ischemia and infarction Maternal death	Preterm birth Low birth weight Small for gestational age infant Shorter gestational age at delivery Reduced birth weight Perinatal infection (HIV, hepatitis, syphilis) Placental aburption	Genitourinary defects Limb reduction Intestinal atresia	Some evidence of adverse behavioral, growth, cognition and learning outcomes, which may be attributable to other social and other perinatal factors.
Amphetamine/ methamphetamine (illicit)	Cardiovascular complications including: • Hypertension • Myocardial ischemia and infarction • Cardiomyopathy Infectious disease (HIV, Hepatitis B and C) Dental disease Adolescent pregnancy	Intrauterine growth restriction Preterm birth Fetal death Earlier gestational age Lower birthweight Smaller head circumference	Cleft Palate	Increased anxiety and depression & attention problems at 3 and 5 years old Poorer cognitive outcomes at 7.5 years old Frontal and striatal brain changes at age 7–15 years old with differential effects by sex
Ecstasy (MDMA)	Limited information Work and social problems	Limited	Cardiovascular Musculoskeletal (clubbed foot) Gastroschisis	Poor motor quality and lower milestone attainment at 4 and 12 months of age Fine and gross motor delays at 24 months of age
Ephedra	Limited information Cardiovascular complications Death Among those with co-existing psychiatric conditions, psychosis, severe depression, mania, suicidal ideation ** Based on data from non-pregnant populations	Limited	Limited	Limited
Synthetic Cathinone (“Bath salts”)	None available	None available	None available	None available

Table 2:

Research gaps in stimulant use among pregnant women

Screening, brief intervention and referral to treatment (SBIRT)
- Proportion of pregnant women who are using illicit and prescription misuse stimulant with universal screening
- Effect of brief intervention among pregnant women at low and moderate risk of stimulant use disorder
- Proportion of women with identified stimulant use disorder referred to treatment

Short and long term outcomes of perinatal stimulant use
- Maternal, perinatal, fetal and childhood outcomes of stimulant use in pregnancy

Treatment studies
- Inclusion of pregnant and postpartum women in pharmacotherapy studies for methamphetamine and cocaine use disorders
- Inclusion of pregnant and postpartum women in behavioral health intervention studies in stimulant use disorders

Health services
- Proportion of pregnant and postpartum women who are able to access substance use treatment
- Impact of family centered care models for stimulant use disorders