Psychotropic drug abuse in pregnancy and its impact on child neurodevelopment: A review

Afshar Etemadi-Aleagha, Maryam Akhgari

ORCID number: Afshar Etemadi-Aleagha 0000-0002-5431-6268; Maryam Akhgari 0000-0002-4126-3398.

Author contributions: Etemadi-Aleagha A contributed to the conception of the research idea, design, paper drafting and revision for important intellectual content; Akhgari M was involved in providing acquisition and interpretation of data, drafting and revision for important intellectual content; all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Country/Territory of origin: Iran

Specialty type: Neurosciences

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an open-access article that was

Afshar Etemadi-Aleagha, Department of Anesthesiology and Intensive Care, Tehran University of Medical Sciences, Tehran 1145765111, Iran

Maryam Akhgari, Legal Medicine Research Center, Legal Medicine Organization, Tehran 1114795113, Iran

Corresponding author: Maryam Akhgari, PhD, Associate Professor, Legal Medicine Research Center, Legal Medicine Organization, No. 2, Misaq Alley, Behesht St, District 12, Tehran 1114795113, Iran. akhgari1349@yahoo.com

Abstract

Substance abuse by women of child-bearing age and fetal in utero drug exposure has increased in the number of infants born with health issues. Prenatal exposure to psychoactive substances can lead to neurological and neurodevelopmental deficits later in life. Useful data concerning the effects of psychoactive drugs on fetal neurodevelopmental status are sparse. Understanding the neurodevelopmental consequences of prenatally drug-exposed children has become a pressing global concern. The aim of this review is to gather current evidence and information on neurodevelopmental outcomes of in utero drug exposure. A literature search was performed on the PubMed, Scopus, and Google Scholar databases using the terms “psychotropic drugs”, “neurodevelopmental consequences”, “prenatal drug exposure”, and “pregnancy”. Available studies on in utero drug exposure were reviewed and found to support the idea that some degree of health issues are present in fetuses and children. Different psychoactive substances have profound neurodevelopmental consequences, such as structural brain changes, poor attention span, Down syndrome, attention deficit hyperactivity disorder, autism spectrum disorder, imbalances in neurotransmitter levels, and many structural deficits. The pervasive use of psychoactive drugs in women of child-bearing age is an important health concern. Further scientific efforts are needed to investigate the effect of prenatal exposure to psychoactive drugs on children.

Key Words: Psychotropic drugs; Pregnancy; Prenatal substance exposure; Brain; Neurodevelopmental outcomes; Fetus

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.
selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/License s/by-nc/4.0/

Received: February 26, 2021
Peer-review started: February 26, 2021
First decision: April 20, 2021
Revised: April 21, 2021
Accepted: November 29, 2021
Article in press: November 29, 2021
Published online: January 9, 2022
P-Reviewer: Matowicka-Karna J
S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Gong ZM

**INTRODUCTION**

Addiction to drugs is defined as the repeated use of addictive substances that cause a set of physiological and behavioral effects. The repeated use of drugs, cravings, and withdrawal symptoms after stopping drug use are among the most important typical symptoms of addiction[1]. The prevalence of the non-medical and recreational use of drugs and substances among women remains at a level comparable to that of men[2]. Alongside the increasing trend of drug abuse, there has been a corresponding rise in the use (and abuse) of licit or illicit drugs in women of child-bearing age[3]. Drug use among pregnant women may result in several medical complications, both for the mother and her child. There are many critical variables involved in the effects of drugs of abuse on fetal brain development. These variables include the duration, timing, and magnitude of exposure, as well as how much of the drug enters the fetus blood and central nervous system (CNS). As the amount of absorbed drug is not equal along different routes of drug administration (oral, inhalation, smoking, and injection), their effects on a fetus’s vital organs and fetal toxicity also differ[1]. Human research on pregnant mothers using illicit drugs has demonstrated associations between substance use and pregnancy loss[1].

There are several issues regarding drug abuse during pregnancy and its impact on child neurodevelopment. There are some practical difficulties in studying human embryos during in utero drug exposure. Drug-dependent mothers often use multiple drugs from different categories with various pharmacologic properties. This situation renders it challenging to study the effect of a single drug on the fetus’s neurodevelopment in isolation. Other factors, such as the mother’s hormones and blood glucose level, also influence the child’s neurodevelopment[4]. However, studies based on self-reports of illicit drug use during pregnancy are subject to an underrepresentation bias[5].

Prenatal drug exposure is a rising global phenomenon with significant variability across countries[6]. Fetal brain development takes place during pregnancy. The first trimester of pregnancy is a particularly important period of development[7]. Exposure to drugs and substances early in life has long-lasting adverse effects on brain structure and function[8]. Embryonic exposure to drugs and addictive substances can change the cellular morphology of cortical neurons. Previous reports have confirmed that the cerebral cortex is greatly affected by drugs. The architecture of neurons, receptor function, and the synaptic plasticity of many inhibitory and excitatory neurons in the marginal system of the midbrain cortex are altered by drug use[9]. Prenatal exposure to drugs is one of the important issues that impact the CNS development of a fetus and, subsequently, his/her future behavior. Experimental and animal studies offer evidence that prenatal neurodevelopmental insults continue to involve fetal, neonatal, infant, and childhood CNS development[9]. Understanding the relationship between prenatal drug exposure and its effects on children’s neurodevelopmental outcomes is a problematic task for researchers[10]. Associations between prenatal drug exposure and neurodevelopmental consequences in children are complicated because of confounding factors such as the type of drug used and its dose, environmental circumstances, and individual genetic profiles. Such circumstances limit researchers’ ability to...
understand the connection between in utero drug exposure and late childhood consequences[9].

Previous studies focused on the fetal health consequences of individual drug classes. The aim of this review is to summarize the effects of different categories of substances abused by pregnant women and their effects on children, including a detailed description of neurodevelopment difficulties.

**DRUG PHARMACOKINETICS DURING PREGNANCY**

Numerous factors play important roles in fetal exposure to drugs including drug dose, maternal drug pharmacokinetic parameters, drug distribution and elimination in the fetus body. However, three main factors determine a drug’s transfer rate from placenta to fetus body; drug lipophilicity, the pH gradient across the placenta, and drug’s protein-binding properties[11]. Non-ionized, low molecular weight and lipid-soluble drugs are freely absorbed from the placenta to the fetus body. Two important factors are responsible for drug equilibration between maternal and fetal blood compartments; concentration gradient (fetal/maternal drug ratio) and the placental blood flow[11]. The metabolic power of the fetus for the metabolism of drugs and substances administered to the mother is not completed during the first 3 mo of fetus life, resulting in the exposure of the fetus to high quantities of drugs[11]. Physiologic changes during pregnancy affect several pharmacokinetic parameters such as absorption, distribution, metabolism, and excretion of drugs[11]. The first pharmacokinetic parameter, absorption, decreases during pregnancy as a result of gastric emptying time reduction as well as the small bowel drug transit time[11]. There is an escalation of maternal plasma volume during pregnancy, which can be increased by 50% during the last trimesters of pregnancy, thus leading to lower plasma concentration of drugs[11,12]. Most psychotropic substances have a lipophilic chemical structure and show a greater volume of distribution during pregnancy[12]. It is important to mention that hormonal induction or inhibition of metabolic processes plays an important role in pharmacokinetic changes of psychoactive substances during pregnancy[12].

**PSYCHOACTIVE DRUGS AND SUBSTANCE CLASSIFICATIONS**

**Cannabis and synthetic cannabinoid receptors agonists**

Cannabis consists of the flowering or fruiting tops of the cannabis plants — its sativa, ruderalis, and indica subspecies contain a number of chemical substances. The most predominant substance with psychoactive properties is delta-9-tetrahydrocannabinol, commonly known as THC. Other cannabinoids are cannabidiol (CBD) and cannabinol (CBN). The term “cannabis” is defined as different products obtained from the cannabis plant.

Marijuana, also known as cannabis, is obtained from plants of the cannabis genus that are members of the Cannabaceae family. The pharmacoologically active ingredients of marijuana are the phytocannabinoids that interact with cannabinoid receptors. Tetrahydrocannabinol (THC) and cannabidiolic acid are two products of cannabinoids. There are many slang and street names for marijuana, including herb, weed, hashish, ganja, and grass. THC is the active ingredient of resin produced from the leaves and buds of female plants. The cannabis plant contains about 500 chemical compounds, 100 of which are structurally and chemically related to THC. These compounds, together with THC, are called cannabinoids[13]. CB1 and CB2 are two known cannabinoid G protein-coupled receptors. CB1 is found on axons and nerve terminals in the CNS[14]. Meanwhile, CB2 receptors are mostly expressed on immune cells[14]. Two active components of the cannabis plant (THC and CBD) are CB1 and CB2 receptor agonists. CB1 receptor agonists mediate decreased neuronal signaling across synapses[15]. Dried leaves of cannabis plant is shown in Figure 1.

**Common routes of administration of cannabis products:** Marijuana inhalation is the fastest route by which THC enters systemic blood circulation. Marijuana inhalation can be performed through smoking, dabbing, or vaporization. Different oral preparations, including drops, cakes, tinctures, candies, snacks, and drinks, are produced as oral marijuana. Rectal and vaginal suppositories are also made from oils and waxes that contain marijuana[15].
Marijuana pharmacokinetics in pregnancy: Maternal use of marijuana has a high frequency due to the perception that marijuana is safe and can be used during pregnancy[16]. Human and animal studies have demonstrated that THC rapidly crosses the placenta and that its concentration in fetal blood correlates with that in maternal blood. A placenta’s normal physiology and transport mechanisms are affected by marijuana. The permeability of the placental barrier to licit and illicit drugs increases due to CBD exposure, thus enhancing fetal exposure to other drugs and poisons. Other human studies have confirmed that prenatal exposure to cannabis reduces blood flow that is essential to supply the placenta. After oral administration, the amount of THC absorbed exceeds 90%. However, due to first-pass hepatic metabolism, its bioavailability is limited to less than 20%. In contrast, after marijuana smoking, THC bypasses the first-pass hepatic metabolism, resulting in highly irregular bioavailability. However, its concentration reduces due to losses through sidestream smoke, absorption by cigarette butts, and pyrolysis[17,18].

Effect of cannabis use in pregnancy and childhood outcomes: Studies on the effects of marijuana in pregnancy are confounded by nutritional inadequacy and multi-substance abuse that can show synergistic effects[19]. Animal and human studies on the effect of THC in fetal brains have demonstrated structural brain changes, especially in the nucleus accumbens[20,21]. One previous study showed that marijuana use was significantly associated with stillbirth, spontaneous preterm birth, and decreased birth weight[22]. Cannabis use was evidenced by tetrahydrocannabinolic acid positive screens in umbilical cord homogenate. This result was confounded by concurrent maternal tobacco use[23].

Prenatal marijuana use has a high prevalence as a recreational drug or to alleviate nausea and morning sickness. Babies exposed to prenatal cannabis suffer from problems associated with neurological development. These problems are manifested as changing responses to visual stimuli, shivering, and high-pitched cry[24]. Memory and skill gap problems are other important difficulties among school-aged children exposed to cannabis in the prenatal phase[25]. Neurologic tests and intelligence quotient (IQ) estimation manifested variable degrees of impairment in visual memory, perception, and language comprehension in different periods of children’s lives. Children also suffered from poor sustained attention and high hyperactivity and impulsivity[26].

A study conducted in Hawaii showed that many birth defects, including Down syndrome, cardiovascular issues, arm and hand defects, and orofacial clefts, are more prevalent among children exposed to cannabis during gestation[27]. Another study in Canada confirmed that congenital defects were more common in territories where cannabis is smoked more often than in other territories[28]. Concerningly, the elevated rates of acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), rhabdomyosarcoma, and neuroblastoma in the pediatric population suggest further implications of cannabinoid-induced genotoxicity[27].

Synthetic cannabinoid receptor agonists: Synthetic cannabinoid receptor agonists are designed substances with structural features that allow binding to cannabinoid receptors. These substances mimic the effects of cannabis but are not licensed for medical use. In an experimental study conducted to evaluate the effect of synthetic cannabinoid receptor agonists on cortical and sub-cortical brain areas across postnatal
development, it was concluded that the administration of synthetic cannabinoid receptors has a disparate effect on neural morphology in adult and adolescent rats. Their results suggest that neural circuits in the adolescent brain may be more vulnerable to drugs[29].

**Opium, opiates, and opioids**

Opium is defined as the coagulated juice obtained from the plant *Papaver somniferum.* There are a number of alkaloids with psychoactive properties which can be extracted from opium. Morphine, codeine, thebaine, papaverine, and noscapine are the major alkaloids in opium. Heroin (diacetylmorphine, diamorphine) is a semi-synthetic opiate obtained from the acetylation of morphine.

**Opioids’ mechanism of action:** The pharmacologic properties of morphine, heroin, and other opiates are mediated through the activation of opioid receptors. There are different types of opioid receptors. Among them, μ (mu) receptors mediate analgesic and behavioral effects[30].

Opioids refer to opiates and their synthetic congeners, which can be synthetic or semi-synthetic. Their pharmacologic properties are similar to those of morphine. Synthetic derivatives of opioids have different chemical structures and can be extremely potent. Fentanyl derivatives, methadone, and buprenorphine are classified as synthetic opioids[30].

**Opioid use during pregnancy and its outcomes:** The prevalence of opioid use among women of child-bearing age has increased dramatically. In utero exposure to opioids can have a direct effect on neuronal development[10]. Before environmental confounding factors influence child neurodevelopment, neurological changes can be observed shortly after birth in opioid-exposed infants[31]. Along with adverse neonatal outcomes associated with prenatal opioid exposure (stillbirth, premature delivery, and reduced gestational age), brain growth and poor neurodevelopmental outcomes are important health issues[32].

However, maternal confounding factors, such as the concomitant use of alcohol and cigarettes, and multi-drug use during pregnancy (and their effects on neurodevelopmental outcomes), should not be neglected[33]. Damage to the central and peripheral nervous systems of fetuses is the leading adverse effect of opioids use in pregnancy[8]. The most significant consequences of opioid exposure on fetal neural development are neural tube defects and neonatal abstinence syndrome[8]. Incomplete closure of neural tube during 4 or 5 wk of embryonic neural tube development is a congenital malformation caused by opioids. It is demonstrating as anencephaly, encephalocele, and spina bifida[8,34]. Opioids can change connections and sizes between different parts of the brain, including the basal ganglia, thalamus, and cerebellar white matter. Also, the myelination process in developing oligodendrocytes is altered as a result of the effect of opioids on the fetus brain[35]. Opioid-exposed children suffer from lower cognitive and psychomotor scores and poor social-emotional consequences during infancy and preschool age. Preschool- and school-age children exposed to opioids during the prenatal period tend to have below-average IQ scores and language development and skills, as well as high attention problem scores. Results of previous findings strengthen the idea that opioid-exposed children suffer from a wide variety of long-term neurodevelopmental disorders. These problems were seen among infants born to opioid-dependent mothers taking methadone[3]. According to previous studies, methadone-exposed infants exhibit a more dysregulated pattern of neurobehavioral disorders at the time of birth in comparison to unexposed infants[3,36].

Prescription opioids are used as pain relievers and as substitutes for opioids in drug rehabilitation programs. However, these groups of substances are commonly abused by women of child-bearing age[8]. Methadone is a highly lipophilic substance with a low molecular weight. It readily crosses the placenta and reaches the embryo. Experimental and animal model studies have demonstrated that methadone has a profound impact on a child’s neuronal development and brain function. It has been confirmed that methadone has deleterious effects at the critical stages of neuronal myelin formation[4,37]. Stoetzer et al[38] indicated that methadone disrupts locomotor activity. Methadone and other opioids have a negative influence on ion channels, thereby altering neuronal network activities. Methadone disrupts the integrity of human cortical organoids in a dose- and stage-dependent manner. Methadone also antagonizes NMDA receptors in human cortical organoids[4].

It has been confirmed that poor attention, regulation, and quality of movement result from in utero methadone exposure. Methadone-exposed infants suffer from excitability, regulation, signs of stress, abstinence, neurological deficits, and intel-
lectual disabilities later in life. Results of follow-up studies in children at 24 mo of age revealed that distinct neurobehavioral profiles, such as poor cognitive and motor development, persist over the first 4.5 years of a child’s life[3,4]. However, there was no difference between infants prenatally exposed to methadone in comparison with unexposed infants at the gestational age.

Stimulants
Amphetamine-type stimulants: The term amphetamine-type stimulants (ATSs) refers to a group of substances that are mostly synthetic. The principal members are amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). ATSs have stimulatory effects on the CNS, as they interfere with the dopamine, norepinephrine, and serotonin systems[30].

Amphetamines mechanism of action: Amphetamine and methamphetamine affect neurotransmitter levels through various mechanisms. The mechanism of ATSs is mainly based on direct interactions with neurons and the information transmitted between them. Each specific substance has its own mechanism of action, but the basic principles remain the same. ATSs increase neurotransmitter concentrations in neuron synapses. On the other hand, ATSs are also classified as non-catecholamine sympathetic drugs that do not have catecholamine chemical structures and do not influence receptors[1]. Once methamphetamine enters the CNS, it releases noradrenaline, dopamine, and serotonin, and it mediates an increase in monoamine concentrations in neuronal cytosols and synapses. Neurotransmitter reabsorption inhibition is another mechanism by which ATSs increase neurotransmitter concentrations in neuronal synapses. Monoamine oxidase (MAO) is an enzyme involved in the degeneration and inactivation of monoamines. The methyl group on the alpha carbon in methamphetamine structure inhibits MAO activity, resulting in an increased monoamine concentration[1]. The combination of these processes stimulates the CNS. Methamphetamine acts mainly via interference with dopaminergic and serotonergic neuronal response pathways. In other words, methamphetamine can be classified as a non-catecholamine sympathetic substance[1].

Methamphetamine pharmacokinetics: Methamphetamine is absorbed freely through the gastrointestinal tract. It passes through the blood-brain barrier (BBB) with greater ease than its less lipophilic analogues, such as amphetamine. Methamphetamine is widely distributed throughout the body. It is metabolized differently in various animal species. In the human body, a substantial amount of methamphetamine is excreted unchanged via urine as a parent drug. Hydroxymethamphetamine is one of the methamphetamine metabolites that is formed via hydroxylation in the liver and excreted in the urine. The other metabolite is amphetamine, which is produced as a result of the N-demethylation of methamphetamine[1].

Neurotoxic effects of methamphetamine: The neurotoxic effects of methamphetamine occur as a result of highly reactive free radical production due to dopamine auto-oxidation. Also, vesicular pool storage depletion to the cytoplasmic compartment in dopaminergic neurons induces intraneuronal oxidation, which is one of the primary causes of dopamine terminal injury[39]. In conclusion, the imbalance among the vesicular, cytoplasmic, and extracellular dopamine pools is important in the neurotoxic action of methamphetamine. After long-term exposure to methamphetamine, dopaminergic receptors are degraded, dopamine production decreases, and withdrawal symptoms arise[40].

Different parts of the brain responsible for pleasure, motor control, and addiction are connected to each other by dopaminergic and serotonergic pathways. Monoamine transporters, such as dopamine, serotonin, and norepinephrine transporters, aid methamphetamine’s entrance to the neuron body. Methamphetamine displaces monoamine pools in vesicular and intracellular compartments, and it facilitates the release of monoamines into the synaptic space[41].

Methamphetamine is a neurotoxic substance that can cause striatal nerve terminal degeneration. Dopamine extracellular concentrations are elevated via the migration of dopamine from intracellular pools to the extracellular space induced by methamphetamine. Methamphetamine exerts its neurotoxic effect via the auto-oxidation of dopamine into highly reactive free radicals[1,39,41]. The primary cause of dopamine terminal injury is the redistribution of dopamine from vesicular stores to the cytoplasmic compartment, which causes intraneuronal oxidation[1,39]. In methamphetamine-addicted subjects and long-term users, reduced dopamine production and a loss of dopaminergic receptors trigger the need to increase the dosage of the abused substance[40]. Methamphetamine-induced hyperthermia is mediated by dopamine...
receptor overactivation. However, as dopamine stores deplete over time, serotonin starts to play the main role. Methamphetamine reduces forebrain serotonin concentrations causing depression and sleep disorders.

**Methamphetamine use during pregnancy and its outcomes:** Women are more sensitive to methamphetamine than men. Unfortunately, methamphetamine use among pregnant women has increased. Pregnancy has an important effect on a woman’s sensitivity to drugs. In addition to malnutrition in addicted pregnant women, sensitivity to some drugs, such as cocaine, increases, sometimes causing sudden fetal death[42,43]. Methamphetamine’s concentration peak, distribution volume, and biological half-life are affected by physiological changes and altered body water volume during pregnancy. Many factors change in the placenta throughout pregnancy. The placenta’s cellular membrane, protein binding, nutrient and oxygen transfer capacity, blood flow rate, and drug permeability to the fetus are strongly affected by drug use[1]. Previous studies have confirmed that methamphetamine passes the placental barrier easily. It was also shown that half of the methamphetamine concentration can be detected in the fetal blood circulatory system when compared to maternal blood[44,45]. Methamphetamine is mainly metabolized in the liver, but the enzymatic system in the fetal liver is not yet able to handle large amounts of drugs. After repeated exposure to methamphetamine, high drug concentrations can be found in fetal plasma[44]. Due to the oxidant activity of methamphetamine and reactive oxygen species production, antioxidant levels are decreased in the embryo during maternal methamphetamine use, resulting in oxidative damage to lipids, proteins, and DNA[46].

Previous studies demonstrated that methamphetamine decreases dopamine and norepinephrine levels, followed by an increase in synaptic activity that produces neurotoxic effects on the CNS. Cui et al[47] showed that methamphetamine combined with monoamine neurotransmitters can disturb fetal brain development.

Issues regarding methamphetamine exposure during the prenatal period are associated with impaired neurological development[48]. Infants suffering from prenatal exposure to methamphetamine show neurobehavioral development manifestations, such as poor movement, electroencephalogram (EEG) changes, elevated stress levels, and physical tension[48,49]. Other studies confirmed low birth weight, stillbirth, and intrauterine growth retardation in methamphetamine-exposed children[30]. Fetus brain structure can also be affected by methamphetamine. Previous studies offer evidence of decreased volumes of subcortical structures such as the putamen, globus pallidus, caudate nucleus, and hippocampus; smaller striatum; and fewer dopamine (D2) receptors due to prenatal methamphetamine exposure[51]. However, these children do not suffer from language problems or low IQ[52]. Young school-aged children exposed to methamphetamine during their prenatal life exhibit problems related to adapting with their peers and cognition. They show anxiety, emotional instability, aggression, and personality disorders such as attention deficit hyperactivity disorder (ADHD)[53].

**Coca and cocaine**

Cocaine is obtained from the plant *Erythroxylon coca*. It consists of different kinds of alkaloids, including cocaine (the main psychoactive substance of coca leaves), benzoylcegonine, and ecgonine[30]. Cocaine exerts its stimulant activity by affecting the brain’s dopamine, norepinephrine, and serotonin neurotransmitter systems. However, cocaine’s effect on the level of dopamine is more pronounced than that of methamphetamine and amphetamine[30].

**Cocaine’s mechanism of action:** Cocaine binds to monoamine transporters in the fetal brain. Animal model studies have described decreased dopaminergic, beta-adrenergic, and serotonergic receptor expressions in the embryonic brain following prenatal cocaine exposure[5]. Long-term repercussions of cocaine exposure have been found in GABA and glutamate neurotransmitters systems, resulting in an increase in the numerical density and anatomical alterations of glutamatergic neurons. These changes suggest alterations in neocortical connectivity that can cause behavioral and cognitive deficits[5,54].

**Cocaine use during pregnancy and its outcomes:** Recent studies report that cocaine use among pregnant women continues to be a public health concern. Fetal cocaine exposure during pregnancy disrupts brain monoamines, especially dopamine, during a critical stage of brain development. Animal-based and experimental studies permit rigorous and hypothesis-driven explorations of the effect of prenatal cocaine exposure
on brain development. There are some confounding factors in the human-based studies, such as multi-drug use. Multi-drug use is common among cocaine users. They often use alcohol, nicotine, and marijuana with cocaine[5]. Prenatal cocaine exposure can affect early brain development. It causes fetal growth retardation, seizure, respiratory distress, cerebral malformation, and, in some instances, sudden infant death syndrome. An infant’s behavioral profile correlates with the timing of cocaine exposure. Cocaine exposure during the first and second trimesters causes abnormal reflexes, but its exposure during the second and third trimesters induces reductions in motor maturity and muscle tone[5]. Other consequences of prenatal cocaine exposure are disrupted arousal regulation, attention, emotional reactivity, and reward systems[5]. Children exposed prenatally to cocaine have shown specific language and cognitive deficits, behavioral problems, and impaired social development[5,55]. Abnormal brain development can be exhibited as decreased head circumference and microcephaly as a result of high levels of prenatal cocaine exposure. In fact, head circumference is a good predictor of neurobehavioral deficits in prenatal cocaine-exposed children. Magnetic resonance imaging (MRI) of brains revealed size reductions in cortical and subcortical structures, including a smaller caudate, corpus callosum, and pallidum. In contrast, the amygdala’s size increases[56]. Significant reductions in the volume of cortical gray matter, thalamus, and putamen resulted from in utero cocaine exposure[57]. Brain wave activity changes and seizures are other outcomes of prenatal cocaine exposure. Prenatal cocaine-induced seizures continue throughout the child’s initial months of life and, in some cases, even after 6 mo, suggesting long-term neurodevelopmental consequences of early life cocaine exposure[58].

Previous studies have confirmed that cocaine- or heroin-exposed infants are impacted by a combination of drugs (known as cocktails) with a variety of pharmacologic properties[7,59]. Cocaine users often use other substances, such as alcohol and tobacco, simultaneously[7].

Hallucinogens

Hallucinogens are naturally occurring or synthetic substances that induce hallucinations and distortions in consciousness and perception, thinking and feeling, often accompanied by some degree of auditory or visual hallucinations. They are also known as “psychedelics,” and they produce synaesthesia and alter the user’s perception of reality. Hallucinogenic agents fall into different chemical groups, including tryptamine (lysergic acid diethylamide or LSD and psilocin) and phenethylamines (mescaline, the main psychoactive component of peyote cactus). Hallucinogens mediate their hallucinogenic activity through interactions with serotonin receptors.

LSD is one of the most potent hallucinogenic substances. It is derived from lysergic acid, an alkaloid found in a fungus named Claviceps purpurea. LSD’s mechanism of action is similar to those of other hallucinogens. LSD exerts its hallucinogenic effect via its agonistic activity at the serotonin receptor 5-HT2A. Serotonin is a neurotransmitter with biogenic properties. It acts as a neurotrophic agent in neuronal development processes such as neurogenesis and neuronal differentiation[60]. It has been shown that each agent that alters serotonergic signaling is linked to neurodevelopmental disorders such as autism spectrum disorder (ASD), ADHD, depression, and schizophrenia. Previous studies have demonstrated that normal placental structure and function are associated with equilibrium in serotonin signaling[61]. In fact, deficient placental serotonin levels are correlated with fetal growth restriction, anxiogenic behavior, and ASD[61].

Alcohol

Alcohol pharmacokinetics during pregnancy: Alcohol is absorbed readily from the placenta into the fetal bloodstream. Prenatal alcohol exposure begins with the dispersion of alcohol through the placenta to the fetal compartment. The chemical structure of ethanol enables rapid diffusion across the placental barrier and dispersion throughout the body water. The time needed to obtain an equilibrium between fetal and maternal alcohol concentration is one to two hours. Alcohol dehydrogenase is the enzyme responsible for ethanol metabolism in the mother, placenta, fetus, and neonates, though this occurs with different concentrations and activities. Available studies showed that the metabolic capacity of a fetus for ethanol oxidation is limited and that the majority of ethanol metabolism takes place in the maternal body to clear ethanol from the fetal-maternal unit. Small amounts of ethanol can be excreted unchanged through pulmonary excretion and in fetal urine, which can accumulate in amniotic fluid. It has been shown that the reuptake of amniotic fluid by the fetus has a
dramatic effect on the duration of fetal exposure to alcohol[62]. Alcohol (ethanol) use in pregnancy predisposes developing fetuses to health risks and is linked to adverse prenatal outcomes and fetal alcohol spectrum disorder (FASD)[63]. Many pregnancies are unintended. Therefore, a fetus may unintentionally be predisposed to alcohol in utero during critical embryonic development stages. Some health issues of alcohol use during pregnancy are miscarriage, preterm labor, stillbirth, and intrauterine growth restriction[64,65]. Women are more sensitive to alcohol than men due to their greater alcohol absorption and slower metabolism rate. Therefore, women exhibit higher blood alcohol levels than men upon drinking equal amounts of alcohol[63]. There are some varieties in response to alcohol in the fetal and neonatal stages. Several factors, such as the clearance rate of alcohol in the body, genetic variability, fetal developmental sensitivity, time (critical stages of organ formation), duration of alcohol and multi-drug use, influence the dose-response relationship between the amount of alcohol consumed during pregnancy and child health outcomes.

Alcohol use during pregnancy and its outcomes: Intrauterine alcohol exposure is associated with various fetal structural anomalies, including renal, cardiac, and craniofacial malformations. Children sometimes have complications with vision, hearing, short palpebral fissures, smooth philtrum, and a thin vermilion border of the upper lip as the most important craniofacial structural impairments[66]. Children with FASD may show abnormal facial features; low height and/or weight; and CNS complications such as small head circumference, poor attention and coordination, and hyperactive behaviors.

New psychoactive substances: New psychoactive substances (NPSs) are designer analogues of licit or illicit drugs designed for recreational use. The rapid growth in the global production of NPSs poses a considerable public health risk. These substances have spread in the market under names such as “legal highs”, “research chemicals”, and “bath salts”[67]. However, little is known about the adverse effects, health issues, and psychological properties of these new emerging substances. Safety data on the effect of prenatal exposure to NPSs, their toxicity, and their carcinogenic potential are either not available or limited[68]. Previous studies have pointed out that prenatal exposure to some classes of NPSs represents a risk to fetal health since several newborn outcomes such as neonatal abstinence syndrome have been correlated with these substances[69].

Synthetic cathinones have beta-keto-phenethylamine chemical structures. Their structure and mechanism of action are similar to those of ATS. Mephedrone, 3,4-methylenedioxypyrovalerone (MDPV), and methylone are classified as synthetic cathinones. It has been reported that mephedrone exposure during the gestational phase boosts the risk of low birth weight and stillbirth. Salimi et al.[70]’s study on animal models showed that repeated use of mephedrone induces hippocampal damage, resulting in learning and memory process impairment. Table 1 shows different psychotropic drugs that are commonly used during pregnancy.

CONCLUSION

Pregnancy evolves a myriad of physiological variations in body organs that result in unavoidably significant changes in drug delivery to the fetus. Notably, many licit and illicit psychoactive drugs are designed to reach the brain and penetrate human barriers such as the BBB and the placenta (thus reaching the fetus body). Substance use during pregnancy is associated with an increased risk of neurodevelopmental disorders. Drugs may have subtle outcomes in the late fetal development period when the main organs are formed. Some of these harmful consequences are altered brain formation, imbalanced neurotransmitter volume, changes in receptor expression, and unusual fetal growth patterns. Taken together, findings from previous studies suggest that being born to a drug abuser is a reliable indicator for later neurodevelopmental issues.

Further research is needed on the amount and timing of substance use during pregnancy and childhood health consequences. As NPSs are not categorized as controlled substances in many countries, the effects of prenatal exposure to these psychoactive chemicals and their neurodevelopmental outcomes are obscure and should be considered further.
**Table 1** Commonly used psychotropic drugs during pregnancy

| Drug classification | Drugs | Common forms | Routes of administration |
|---------------------|-------|--------------|--------------------------|
| **Marijuana**       | Hashish | Greenish-gray mixture of dried different parts of cannabis plant; resin (hashish) or sticky, black liquid (hash oil) | Smoking, dabbing, or vaporization; Eaten (drops, cakes, tinctures, candies, snacks, and drinks); Suppositories |
| **Opium**           | Heroin | Sticky brown gum; White or brownish powder, or black substance known as “black tar”; Colorful methadone and tramadol tablets with imprinted logos, capsules, powder, liquid | Injected, smoked, snorted; Swallowed |
| **Amphetamine-type stimulants** | (Amphetamine, Methamphetamine, Ecstasy) | White powder, crystal or shiny blue-white “rocks”; Colorful ecstasy tablets with imprinted logos, capsules; White powder and rock crystal cocaine | Snorted, smoked, injected, swallowed |
| **LSD, psilocin mescaline (peyote)** | | Decorated squares of absorbent paper that LSD has been added to, Tablet, capsule, clear liquid; small pills (dots); Peyote cacti | Swallowed, absorbed through mouth tissues (paper squares); Mixed in food or brewed as tea |
| **Ethyl alcohol**   |       | Alcoholic beverages with different alcohol content | Ingested |

LSD: Lysergic acid diethylamide.

**Limitations**

The majority of the previous studies focused on early neurodevelopment, thereby limiting assessment of long-term impacts of prenatal drug exposure.

**REFERENCES**

1. **Tomášková A, Šlamberová R, Černá M. Influence of Prenatal Methamphetamine Abuse on the Brain. Epigenomes 2020; 4: 1-4** [DOI: 10.3390/epigenomes4030014]
2. **Women and Drugs, Drug use, drug supply and their consequences. World Drug Report 2018 (United Nations publication, Sales No. E.18.XI.9). Available from: https://www.unodc.org/documents/hiv-aids/publications/drugs_abuse_problem_web.pdf**
3. **Woudes TA, Woodward LJ. Neurobehavior of newborn infants exposed prenatally to methadone and identification of a neurobehavioral profile linked to poorer neurodevelopmental outcomes at age 24 months. PLos One 2020; 15: e0240905 [PMID: 33064777 DOI: 10.1371/journal.pone.0240905]**
4. **Yao H, Wu W, Cerf I, Zhao HW, Wang J, Negraes PD, Muotri AR, Haddad GG. Methadone interrupts neural growth and function in human cortical organoids. Stem Cell Res 2020; 49: 102065 [PMID: 33137567 DOI: 10.1016/j.scr.2020.102065]**
5. **Martin MM, Graham DL, McCarthy DM, Bhide PG, Stanwood GD. Cocaine-induced neurodevelopmental deficits and underlying mechanisms. Birth Defects Res C Embryo Today 2016; 108: 147-173 [PMID: 27345015 DOI: 10.1002/bdr2.21132]**
6. **Falsaperla R, Zaami S, Aguglia MG, Romano C, Suppiej A, Meno L. Neurophysiological monitoring in neonatal abstinence syndrome from cocaine. Ann Ist Super Sanita 2020; 56: 390-396 [PMID: 32959806 DOI: 10.4415/ANN_20_03_18]**
7. **Singer LT, Chambers C, Coles C, Julie Kable. Fifty Years of Research on Prenatal Substances: Lessons Learned for the Opioid Epidemic. Adv Res Sci 2020; 1: 223-234 [DOI: 10.1007/s42844-020-00021-7]**
8. **Li XL, Guo YH, Wei ST, Chen J, Wu YB. Research progress on the influence of opioids on fetal neurodevelopment during pregnancy. Life Res 2020; 3: 68-77 [DOI: 10.12032/life2020-0424-301]**
9. **Corsi DJ, Donelle J, Sucha E, Hawkens S, Hsu H, El-Chaar D, Binaire L, Fell D, Wen SW, Walker M. Maternal cannabis use in pregnancy and child neurodevelopmental outcomes. Nat Med 2020; 26: 1536-1540 [PMID: 32778828 DOI: 10.1038/s41591-020-1002-5]**
10. **Lee SJ, Bora S, Austin NC, Westerman A, Henderson JMT. Neurodevelopmental Outcomes of Children Born to Opioid-Dependent Mothers: A Systematic Review and Meta-Analysis. Acad Pediatr 2020; 20: 308-318 [PMID: 31734383 DOI: 10.1016/j.acap.2019.11.005]**
11. **Kokras N, Sotirioupolos MG, Poulgiannopoulou E, Dalla C. Maternal and Infant Pharmacokinetics of Psychotropic Medications During Pregnancy and Lactation. In: Uguz F, Orsolini L, editors. Perinatal Psychopharmacology. Springer, Cham. 2019: 17-35 [DOI: 10.1007/978-3-319-92919-4_2]**
12 Chisolm MS, Payne JL. Management of psychotropic drugs during pregnancy. *BMJ* 2016; 532: h5918 [PMID: 26761406 DOI: 10.1136/bmj.h5918]

13 Thompson R, DeJong K, Lo J. Marijuana Use in Pregnancy: A Review. *Obstet Gynecol Surv* 2019; 74: 415-428 [PMID: 31343707 DOI: 10.1097/OGX.0000000000000685]

14 Lu HC, Mackie K. An Introduction to the Endogenous Cannabinoid System. *Biol Psychiatry* 2016; 79: 516-525 [PMID: 26698193 DOI: 10.1016/j.biopsych.2015.07.028]

15 McCartney D, Arkell TR, Irwin C, McGregor IS. Determining the magnitude and duration of acute Δ²-tetrahydrocannabinol (Δ²-THC)-induced driving and cognitive impairment: A systematic and meta-analytic review. *Neurosci Biobehav Rev* 2021; 126: 175-193 [PMID: 33497785 DOI: 10.1016/j.neubiorev.2021.01.003]

16 Jarlenski M, Koma JW, Zank J, Bodnar LM, Bogen DL, Chang JC. Trends in perception of risk of regular marijuana use among US pregnant and nonpregnant reproductive-aged women. *Am J Obstet Gynecol* 2017; 217: 705-707 [PMID: 28843740 DOI: 10.1016/j.ajog.2017.08.015]

17 Feinshtein V, Erez O, Ben-Zvi Z, Elisar T, Sheizaf B, Sheiner E, Holberg G. Cannabidiol enhances xenobiotic permeability through the human placental barrier by direct inhibition of breast cancer resistance protein: an ex vivo study. *Obstet Gynecol* 2013; 209: 573.e1-573.e15 [PMID: 23933222 DOI: 10.1016/j.obgyn.2013.08.005]

18 Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol* 2018; 84: 2477-2482 [PMID: 30001569 DOI: 10.1111/bcp.13710]

19 Metz TD, Stickrath EH. Marijuana use in pregnancy and lactation: a review of the evidence. *Am J Obstet Gynecol* 2015; 213: 761-778 [PMID: 25986032 DOI: 10.1016/j.ajog.2015.05.025]

20 Kolb B, Gorny G, Limebeer CL, Parker LA. Chronic treatment with Delta-9-tetrahydrocannabinol alters the structure of neurons in the nucleus accumbens shell and medial prefrontal cortex of rats. *Synapse* 2006; 59: 429-436 [PMID: 16881072 DOI: 10.1002/syn.20313]

21 Gilman JM, Kuster JK, Lee S, Lee MJ, Kim BW, Lee MJ, Holberg G. Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. *J Neurosci* 2014; 34: 5529-5538 [PMID: 24741043 DOI: 10.1523/JNEUROSCI.4745-13.2014]

22 Gunn JK, Rosales CB, Center KE, Uñez A, Gibson CJ, Ehiri JE. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. *BMJ Open* 2016; 6: e009986 [PMID: 27048634 DOI: 10.1136/bmjopen-2015-009986]

23 Leenaqz SY, Dekker GA, McCowan LM, Kenny LC, Myers JE, Simpson NA, Poston L, Roberts CT; SCOPE Consortium. Maternal marijuana use has independent effects on risk for spontaneous preterm birth but not on other common late pregnancy complications. *Reprod Toxicol* 2016; 62: 77-86 [PMID: 27142189 DOI: 10.1016/j.reprotox.2016.04.021]

24 de Moraes Barros MC, Guinsburg R, Mitsuhiro S, Chalem E, Larjaneira RR. Neurobehavioral profile of healthy full-term newborn infants of adolescent mothers. *Early Hum Dev* 2008; 84: 281-287 [PMID: 17766063 DOI: 10.1016/j.earlhumdev.2007.07.001]

25 Leech SL, Larkby CA, Day R, Day NL. Predictors and correlates of high levels of depression and anxiety symptoms among children at age 10. *J Am Acad Child Adolesc Psychiatry* 2006; 45: 223-230 [PMID: 16429093 DOI: 10.1097/01.chi.0000184930.18552.4d]

26 Fried PA. The Ottawa Prenatal Prospective Study (OPPS): methodological issues and findings--it's easy to throw the baby out with the bath water. *Life Sci* 1995; 56: 2155-2168 [PMID: 7539879 DOI: 10.1016/0024-3205(95)00234-2]

27 Taormina MK. MSMA Should Embrace Scientific Cannabis Education. *Mo Med* 2020; 117: 529-530 [PMID: 33311777]

28 Reece AS, Hulse GK. Canadian Cannabis Consumption and Patterns of Congenital Anomalies: An Ecological Geospatial Analysis. *J Addict Med* 2020; 14: e195-e210 [PMID: 32187114 DOI: 10.1097/ADM.0000000000000638]

29 Carvalho AF, Reyes BA, Ramalhosa F, Sousa N, Van Bockstaele EJ. Repeated administration of a synthetic cannabinoid receptor agonist differentially affects cortical and accumbal neuronal morphology in adolescent and adult rats. *Brain Struct Funct* 2016; 221: 407-419 [PMID: 25348266 DOI: 10.1007/s00429-014-0914-6]

30 Terminology and Information on Drugs, Third edition. United Nations Office on Drugs and Crime publication. May 2016. Sales No. E.16.XI.8. Available from: https://www.unodc.org/documents/scientific/Terminology_and_Information_on_Drugs_E_3rd_edition.pdf

31 Monnelly VJ, Anblagan D, Quigley A, Cabez MB, Cooper ES, MacIer J, Semple SI, Bastin ME, Boardman JP. Prenatal methadone exposure is associated with altered neonatal brain development. *Neuroimage Clin* 2018; 18: 9-14 [PMID: 29326869 DOI: 10.1016/j.neuroimageclin.2017.12.033]

32 Monnelly VJ, Hamilton R, Chappell FM, MacIer J, Boardman JP. Childhood neurodevelopment after prescription of maintenance methadone for opioid dependency in pregnancy: a systematic review and meta-analysis. *Dev Med Child Neurol* 2019; 61: 750-760 [PMID: 30511742 DOI: 10.1111/dmcn.14117]

33 Norgaard M, Nielsen MS, Heide-Jørgensen U. Birth and Neonatal Outcomes Following Opioid Use in Pregnancy: A Danish Population-Based Study. *Subst Abuse* 2015; 9: 5-11 [PMID: 26512202 DOI: 10.4137/SART.S23547]

34 Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. *Obstet Gynecol* 2013; 122: 838-844 [PMID: 24084542 DOI: 10.1097/AOG.0b013e3182784d6e]
Etemadi-Aleagha A et al. Neurodevelopmental outcomes of in utero drug exposure

10.1097/AOOG.0b013e3182a6643c

35 Caritis SN, Parangi A. Opioids affect the fetal brain: reframing the detoxification debate. *Am J Obstet Gynecol* 2019; 221: 602-608 [PMID: 31323217 DOI: 10.1016/j.ajog.2019.07.022]

36 Heller NA, Logan BA, Morrison DG, Paul JA, Brown MS, Hayes MJ. Neonatal abstinence syndrome: Neurobehavior at 6 weeks of age in infants with or without pharmacological treatment for withdrawal. *Dev Psychobiol* 2017; 59: 574-582 [PMID: 28616104 DOI: 10.1002/dev.21532]

37 Vestal-Laborie AA, Eschenroeder AC, Bigbee JW, Robinson SE, Sato-Bigbee C. The opioid system and brain development: effects of methadone on the oligodendrocyte lineage and the early stages of myelination. *Dev Neurosci* 2014; 36: 409-421 [PMID: 25138998 DOI: 10.1159/000356074]

38 Stoetzer C, Kistner K, Stüber T, Wirths M, Schulze V, Doll T, Foardi N, Wegner F, Ahrens J, Leffler A. Methadone is a local anaesthetist-like inhibitor of neuronal Na+ channels and blocks excitability of mouse peripheral nerves. *Br J Anaesth* 2015; 114: 110-120 [PMID: 25012584 DOI: 10.1093/bja/aeu206]

39 Bourque M, Liu B, Dluzen DE, Di Paolo T. Sex differences in methamphetamine toxicity in mice: effect on brain dopamine signaling pathways. *Psychoneuroendocrinology* 2011; 36: 955-969 [PMID: 21236583 DOI: 10.1016/j.psyneuen.2010.12.007]

40 Hollerman JR, Schultz W. Dopamine neurons report an error in the temporal prediction of reward during learning. *Nat Neurosci* 1998; 1: 304-309 [PMID: 10195164 DOI: 10.1038/1124]

41 Numachi Y, Ohara A, Yamashita M, Fukushima S, Kobayashi H, Hata H, Watanabe H, Hall FS, Lesch KP, Murphy DL, Uhl GR, Sora I. Methamphetamine-induced hyperthermia and lethal toxicity: role of the dopamine and serotonin transporters. *Eur J Pharmacol* 2007; 572: 120-128 [PMID: 17673199 DOI: 10.1016/j.ejphar.2007.06.022]

42 Maciuchová E, Nohejlová K, Slamberová R. Gender differences in the effect of adult amphetamine on cognitive functions of rats prenatally exposed to methamphetamine. *Behav Brain Res* 2014; 270: 8-17 [PMID: 24796632 DOI: 10.1016/j.bbr.2014.06.040]

43 Behnke M, Smith VC; Conference on Substance Abuse; Conference on Fetus and Newborn. Prenatal substance abuse: short- and long-term effects on the exposed fetus. *Pediatrics* 2013; 131: e1009-e1024 [PMID: 23439891 DOI: 10.1542/peds.2012-3931]

44 Dattel BJ. Substance abuse in pregnancy. *Semin Perinatol* 1990; 14: 179-187 [PMID: 2187251]

45 Rambousek L, Kacer P, Syslova K, Bumba J, Bubenikova-Valesova V, Slamberova R. Sex differences in methamphetamine pharmacokinetics in adult rats and its transfer to pups through the placental membrane and breast milk. *Drug Alcohol Depend* 2014; 139: 138-144 [PMID: 24726427 DOI: 10.1016/j.drugalcdep.2014.03.023]

46 Neri M, Bello S, Turillazzi E, Riezzo I. Drugs of abuse in pregnancy, poor neonatal development, and future neurodegeneration. Is oxidative stress the culprit? *Curr Pharm Des* 2015; 21: 1358-1368 [PMID: 25564389 DOI: 10.2174/1381612821666150105124510]

47 Cui C, Sakata-Haga H, Ohta K, Nishida M, Yashiki M, Sawada K, Fukui Y. Histological brain alterations following prenatal methamphetamine exposure in rats. *Congenit Anom (Kyoto)* 2006; 46: 180-187 [PMID: 17096818 DOI: 10.1111/j.1744-4520.2006.00126.x]

48 Šlamberová R. Review of long-term consequences of maternal methamphetamine exposure. *Physiol Res* 2019; 68: S219-S231 [PMID: 31928040 DOI: 10.33549/physiorex.934360]

49 Kiblawi ZN, Smith LM, Diaz SD, LaGasse LL, Derauf C, Newman E, Shah R, Arria A, Huestis M, Haning W, Strauss A, Dellagrotta S, Dansereau LM, Neal C, Lester B. Prenatal methamphetamine exposure and neonatal and infant neurobehavioral outcome: results from the IDEAL study. *Subst Abus* 2014; 35: 68-73 [PMID: 24589296 DOI: 10.1080/08998054.2013.814614]

50 Little BB, Snell LM, Gilstrap LC 3rd. Methamphetamine abuse during pregnancy: outcome and fetal effects. *Obstet Gynecol* 1988; 72: 541-544 [PMID: 3419732]

51 Chang L, Smith LM, LoPresti C, Yonekura ML, Kao J, Walot I, Ernst T. Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. *Psychiatry Res* 2004; 132: 95-106 [PMID: 15598544 DOI: 10.1016/j.psychres.2004.06.004]

52 Chakraborty A, Anstice NS, Jacobs RJ, LaGasse LL, Lester BM, Woulfes TA, Thompson B. Prenatal exposure to recreational drugs affects global motion perception in preschool children. *Sci Rep* 2015; 5: 16921 [PMID: 26581958 DOI: 10.1038/srep16921]

53 Kiblawi ZN, Smith LM, LaGasse LL, Derauf C, Newman E, Shah R, Arria A, Huestis M, Dellagrotta S, Dansereau LM, Neal C, Lester B. The effect of prenatal methamphetamine exposure on attention as assessed by continuous performance tests: results from the Infant Development, Environment, and Lifestyle study. *J Dev Behav Pediatr* 2013; 34: 31-37 [PMID: 23270506 DOI: 10.1097/DBP.0b013e3182277a1ce5]

54 McCarthy DM, Kabir ZD, Bhide PG, Kosofsky BE. Effects of prenatal exposure to cocaine on brain structure and function. *Prog Brain Res* 2014; 211: 277-289 [PMID: 24968785 DOI: 10.1016/B978-0-444-63425-2-00012-X]

55 Bada HS, Das A, Bauer CR, Shankaran S, Lester B, LaGasse L, Hammond J, Wright LL, Higgins R. Impact of prenatal cocaine exposure on child behavior problems through school age. *Pediatrics* 2007; 119: e348-e359 [PMID: 17272597 DOI: 10.1542/peds.2006-1404]

56 Rao H, Wang J, Giannetta J, Korczykowski M, Shera D, Avants BB, Gee J, Detre JA, Hurt H. Altered resting cerebral blood flow in adolescents with in utero cocaine exposure revealed by perfusion functional MRI. *Pediatrics* 2007; 120: e1245-e1254 [PMID: 17974718 DOI: 10.1542/peds.2006-2596]

57 Akuz N, Kekapure MV, Liu J, Sheinkopf SJ, Quinn BT, Lala MD, Kennedy D, Makris N, Lester...
BM, Kosofsky BE. Structural brain imaging in children and adolescents following prenatal cocaine exposure: preliminary longitudinal findings. Dev Neurosci 2014; 36: 316-328 [PMID: 24994509 DOI: 10.1155/000362685]

58 Kramer LD, Locke GE, Ogunyemi A, Nelson L. Neonatal cocaine-related seizures. J Child Neurol 1990; 5: 60-64 [PMID: 2299141 DOI: 10.1177/08830738900500115]

59 Akhgar M, Etemadi-Aleagha A, Jokar F. Street level Heroin, an overview on its components and adulterants. In: Preedy VR, editor. Neuropathology of drug addictions and substance misuse volume 1: Foundations of understanding, tobacco, alcohol, cannabinoids and opioids. United Kingdom: Academic Press, 2016: 867-877 [DOI: 10.1016/B978-0-12-800213-1.00081-X]

60 Carvajal-Oliveros A, Campusano JM. Studying the Contribution of Serotonin to Neurodevelopmental Disorders. Can This Fly? Front Behav Neurosci 2020; 14: 601449 [PMID: 33510625 DOI: 10.3389/fnbeh.2020.601449]

61 Rosenfeld CS. Placental serotonin signaling, pregnancy outcomes, and regulation of fetal brain development. Biol Reprod 2020; 102: 532-538 [PMID: 31711155 DOI: 10.1093/biolre/ioz204]

62 Burd L, Blair J, Dropps K. Prenatal alcohol exposure, blood alcohol concentrations and alcohol elimination rates for the mother, fetus and newborn. J Perinatol 2012; 32: 652-659 [PMID: 22595965 DOI: 10.1038/jp.2012.57]

63 Dejong K, Olyaei A, Lo JO. Alcohol Use in Pregnancy. Clin Obstet Gynecol 2019; 62: 142-155 [PMID: 30575614 DOI: 10.1097/GRF.0000000000000414]

64 Henderson J, Gray R, Brocklehurst P. Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. BJOG 2007; 114: 243-252 [PMID: 17233797 DOI: 10.1111/j.1471-0528.2006.01163.x]

65 Muggli E, Matthews H, Penington A, Claes P, O’Leary C, Forster D, Donath S, Anderson PJ, Lewis S, Nagle C, Craig JM, White SM, Elliott EJ, Halliday J. Association Between Prenatal Alcohol Exposure and Craniofacial Shape of Children at 12 Months of Age. JAMA Pediatr 2017; 171: 771-780 [PMID: 28586842 DOI: 10.1001/jamapediatrics.2017.0778]

66 Streissguth AP, Aase JM, Craner SK, Randels SP, LaDue RA, Smith DF. Fetal alcohol syndrome in adolescents and adults. JAMA 1991; 265: 1961-1967 [PMID: 2008025]

67 Lo Faro AF, Di Trana A, La Maida N, Tagliabracci A, Giorgetti R, Busardò FP. Biomedical analysis of New Psychoactive Substances (NPS) of natural origin. J Pharm Biomed Anal 2020; 179: 112945 [PMID: 31704129 DOI: 10.1016/j.jpba.2019.112945]

68 Higgins K, O’Neill N, O’Hara L, Jordan JA, McCann M, O’Neill T, Clarke M, Kelly G, Campbell A. New psychoactives within polydrug use trajectories-evidence from a mixed-method longitudinal study. Addiction 2021; 116: 2454-2462 [PMID: 33506985 DOI: 10.1111/add.15422]

69 García-Algar O, Vall O, Alameda F, Puig C, Pellegrini M, Pacifici R, Pichini S. Prenatal exposure to arecoline (areca nut alkaloid) and birth outcomes. Arch Dis Child Fetal Neonatal Ed 2005; 90: F276-F277 [PMID: 15846024 DOI: 10.1136/adc.2004.061325]

70 Salimi A, Kazemnezad M, Mohammadzadeh Asl B, Jokar F, Jamali Z, Pourmahmoud J. Mephedrone as a new synthetic amphetamine induces abortion, morphological alterations and mitochondrial dysfunction in mouse embryos. Toxin Rev 2020 [DOI: 10.1080/15569543.2020.1803358]
