

The impact on Neurodevelopment of Drugs' Assumption

Cattai Evelyn*, Rallo Alice*

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**Bachelor's degree in Speech and Language Therapy, Padova University*

Abstract. Drugs assumption during pregnancy is a serious risk factor for the neurodevelopment of the fetus, before and after birth. The overall incidence of pregnant women taking illegal drugs is rapidly increasing, partly due to widespread legalization and increasing social acceptance and accessibility. The consequences can occur in the child in the form of neonatal withdrawal syndrome or even years later in childhood. Among the serious effects caused by drugs assumption are the risk of abortion, preterm birth, malformations, and brain damage in the fetus. The factors responsible for fetal damage depend on the type of substances taken and their quantity: the review investigates the consequences of the intake of amphetamines, cannabinoids, the concomitant use of alcohol and cannabinoids (SAC) and cocaine. The main effects of these substances on the mother during pregnancy are shown in Table 1. Pregnant users of illicit drugs, regardless of their country of origin, are more likely to be socially disadvantaged. Moreover, they are usually younger and less likely to seek timely prenatal care. Drug addicts statistically have lower family incomes and rarely have access to affordable health insurance or receive economical support from their families or partners. Therefore, adverse psychosocial conditions are often related to a more frequent intake of illicit substances. More information on the potential risks of prenatal use of substances is considered necessary to encourage women to abstain from drug usage in pregnancy. Furthermore, a greater investment in research is needed, since today there are still several limitations in the literature.

	<i>Description</i>	<i>Effects</i>
Amphetamines	Neurostimulants and neurotoxins	Risk of abortion, preterm birth, smaller head circumferences, low birth weight, lethargy, poor nutrition, drowsiness, behavioral problems
Cannabis	Psychoactive substance	Infertility, risk of miscarriage, abnormal embryo development, neurocognitive and neuropsychiatric disorders, aggressive behavior and attention deficits, abnormal verbal and visual reasoning ability, hyperactivity, short-term memory loss, reduced motor development, more lethargy
SAC	Concomitant use of alcohol and cannabinoids	Reduced VEGF growth factor expression, inhibits angiogenesis, anger, confusion and anxiety, psychosis, ADHD, provocative oppositional disorder and depression
Cocaine	Ototoxic psychoactive substance	Microcephaly, vascular insults, cognitive disabilities, pragmatic difficulties, dysfunction of both peripheral and central auditory systems

Table 1. Use of toxic substances and effects during the pre- and post-natal period.

Neonatal withdrawal syndrome

Neonatal withdrawal syndrome occurs with the sudden deprivation of a substance capable of giving physical dependence, which has been taken by the mother during pregnancy. The severity of neonatal withdrawal syndrome is related to the type of drug used, the amounts taken and the duration of fetal exposure to the substance. The symptoms involve the central and autonomic nervous system and the digestive system and can manifest themselves early, 24/48 hours after birth, or later, after 5/10 days of life of the newborn. Symptoms include tremor and irritability, seizures, vomiting, diarrhea, dehydration, fever and sweating, accelerated breathing, inconsolable crying, and difficulty in feeding. This is one of the many consequences of illicit drug use by women during pregnancy, which in turn causes harmful cascading effects during the development of the child. (Jole Rechichi, 2021)

Amphetamines

Amphetamines are neurostimulants and neurotoxins, they are also some of the most common illicit drugs in the world. They increase the state of wakefulness and attention, and they decrease appetite and fatigue. Users have a very high risk of psychiatric co-morbidity. Furthermore, some evidence suggests that perinatal exposure to amphetamine is associated with poor pregnancy outcomes. Pregnant users of illegal amphetamines, regardless of their country of origin, are more likely to be socially disadvantaged than other drug users. They are usually younger, less likely to seek timely prenatal care, and have lower family incomes. In addition, they are less likely to be insured privately or have support from their partner and family. Concurrent psychiatric morbidities, particularly depression and anxiety, are twice as common in pregnant users of illegal amphetamines as in other drug-using mothers. Amphetamines have been shown to be transferred through the maternal-fetal circulation and are therefore easily detectable and quantifiable in the umbilical cord, placenta, and amniotic fluid. The lack of a capillary network and the absence of an endothelial barrier on the maternal side of the placenta, facilitates

the transfer of nutrients and oxygen and of substances that are ingested by the mother, including drugs. Exposure to amphetamines also increases the risk of placental bleeding and is often the cause of preterm labor. The highest drug concentrations are found in the fetal lungs, followed by placenta, kidneys, intestines, liver, brain, and heart. It is often observed that infants exposed to amphetamine have smaller head circumferences, low birthweight, lethargy, poor nutrition and drowsiness. In addition, amphetamines inhibit the release of prolactin and can reduce the production of breast milk. These complications induced by the intake of amphetamines by pregnant mothers may have consequences during development: behavioral problems, in particular aggression, are manifested especially in preteens, causing serious difficulties in social adaptation. (J L Oei et al., 2012)

Cannabis

Cannabis is the most used illegal drug in the United States and around the world. The prevalence of cannabis use is increasing, especially among people of reproductive age. The biological effects of cannabis are mediated by the endocannabinoid system. Published studies have reported the presence of cannabinoid receptors in the male and female reproductive tracts, sperm, and placenta, suggesting that the endocannabinoid system plays an important role in the regulation of reproduction. Currently, the existing literature suggests that cannabis can influence the reproductive female health, including the secretion of the hormones FSH and LH, ovulation and menstrual cycles. Moreover, cannabis users tend to have more anovulatory cycles than non-users (43% vs 15%). In female patients, cannabis use has therefore been associated with infertility, increased risk of miscarriage, high stillbirth rate and abnormal embryo development. The exposure to THC in utero has also been shown to affect fetal brain development and increase the risk of neurocognitive and neuropsychiatric disorders. An increase in aggressive behavior and attention deficits was observed in offspring at 18 months of age; other effects are the presence of an abnormal verbal and visual reasoning ability, hyperactivity and impulsivity

which emerged already in preschool children born to mothers who had used THC during pregnancy. These studies have also pointed out the correlation between short-term memory loss and first or second trimester cannabis use. More recently, maternal cannabis use has been associated with an increased incidence of neurobehavioral changes, mental health problems, autism spectrum disorders, intellectual disabilities, and learning disabilities in children. Additionally, THC levels, when cannabis is smoked while breastfeeding, peak in breast milk 1 hour after inhalation and remain detectable for 6 days after use. One study found that newborns exposed to THC in breast milk within the first month of life may have reduced motor development compared to unexposed babies. Other studies have suggested that infants exposed to THC through breast milk experience more lethargy, less frequent feeding, stunted growth, poor sucking, and shorter feeding times. (Jamie O. Lo MD, MCR et al., 2022)

SAC

Alcohol and marijuana, a widespread cannabinoid, are two of the most consumed psychoactive substances by pregnant women, and both substances have been associated with lifelong impacts on fetal neurodevelopment. Concurrent with the increase in cannabis use among the general population, young adults of childbearing age are increasingly involved in the simultaneous use of alcohol and cannabinoids (SAC), which amplifies the pharmacodynamic effects of each drug and increases the craving for both the substances. Exposure to ethanol and cannabinoids during development has been shown to reduce growth factor VEGF expression and inhibit angiogenesis. SAC use is attributed to acute and long-term negative behavioral outcomes. A controlled study of alcohol and/or THC-administration demonstrated that participants who used both substances had experienced wider and more frequent mood changes, anger, confusion, and anxiety, than participants using only one drug or no drug. Long-term behavioral disorders also include symptoms of psychosis, attention deficit hyperactivity disorder (ADHD), oppositional de-

fiant disorder, and depression. (Siara Kate Rouzer et al., 2023)

Cocaine

Cocaine is a psychoactive substance that inhibits the post-synaptic reuptake of catecholamines, dopamine and tryptophan and blocks the permeability of sodium ions, resulting in an anesthetic effect. This substance has both an indirect effect on the fetus by affecting the maternal cardiovascular and autonomic systems, and a direct effect by crossing the placenta and directly affecting the cardiovascular and autonomic systems of the fetus. Prenatal cocaine exposure has been associated with microcephaly, seizures, vascular insults, and frank cerebral malformation. Additionally, this exposure causes mild cognitive impairments when measured at 4 years of age, which can be compensated by a stimulating and sensitive care environment. A "cocaine effect" is also seen in speech and language development: the child with prenatal exposure to cocaine may be at greater risk for language delay or impairment. Neurobehavioral examination of the cocaine-exposed infant reveals impaired organizational status, depressed sensory system, hypertonia, gross tremor, and irritability, including excessive jerking. In the study conducted by Mentis and Lundgren (Michelle Mentis and Kristine Lundgren, 1995), discursive-pragmatic skills, syntactic and semantic development were analyzed in five children with prenatal cocaine exposure (PCE) and in five children from the same community who had no cocaine exposure. The results demonstrated a qualitative difference in the use of language by PCE children, rather than a developmental delay, mainly related to the use of inappropriate pragmatics. Furthermore, acute and gestational exposures to cocaine appear to have specific effects on the auditory nervous system. Neonates with acute cocaine intoxication have prolonged latencies of the absolute and interpeak components of the auditory brainstem response (ABR). These prolonged latencies suggest dysfunction of both the peripheral and central auditory systems. The results of the study by Gritzke & Church (R. Gritzke and M.W. Church, 1988) points out an elevated ABR threshold and abnormal latency

with respect to signal level functions. These data concur with cochlear hearing impairment, suggesting an ototoxic effect. In the research of Cone-Wesson and Spingarn (Barbara Cone-Wesson and Aaron Spingarn, 1993) ABRs were tested in all infants using a click stimulus presented at different frequencies. ABR latency was measured for Waves I, III, and V. There was no effect of cocaine exposure status on Wave I latency, but there were effects on Waves III and V. This finding indicates that cochlear and eighth nerve function were not affected by prenatal cocaine exposure. The prolonged latencies for successive ABR peaks are consistent with cocaine effects on the central nervous system because waves III and V depend on the integrity of the brainstem auditory nuclei including the cochlear nucleus (wave III), olive superior and inferior colliculus (wave V). Latencies between I-V wave peaks were prolonged for PCE infants compared to NE infants, at all stimulus frequencies tested. Furthermore, the latency differences between I-V wave peaks, as a function of exposure status, increase with stimulus frequency. This would suggest that infants with PCE have an increased susceptibility to neural adaptation, possibly due to neurotransmitter reduction causing synaptic inefficiency or due to immature myelination. Johnson et al. (Jeanne M. Johnson et al., 1997) speak of a "cumulative synergistic effect" regarding prenatal polydrug exposure (including cocaine, alcohol, tobacco, and marijuana), poor prenatal care, low birth weight, adverse effects of living with an addicted parent, and other uncontrolled variables that could influence the language development. The strong effect of the home environment in ameliorating the effects of prenatal cocaine exposure

suggests that a family-focused approach to cognitive, linguistic, and social-emotional habilitation would be beneficial to all. (Barbara Cone-Wesson, 2005)

Conclusion

Drugs can affect the development of children of mothers with an illegal-drug addiction. Those consequences consist in the minor or altered development of the various components and functions of the organism. We would like to highlight how the use of cocaine can significantly modify the development of the newborn's hearing and language skills. US medical sources recommend that pregnant women should be warned against the potential risks of prenatal use of cannabis and encouraged to abstain from use in pregnancy and while breastfeeding. However, the persistent high drug use is partly due to patients not knowing for sure how safe it is to use prenatal cannabis. Furthermore, healthcare professionals do not always adequately advise or educate cannabis patients and retailers, who promote cannabis as a safe, natural and effective method of alleviating pregnancy symptoms (Jamie O. Lo MD, MCR et al., 2022). Moreover, a greater investment of resources in the research field is needed, since literature is scarce: sample sizes are relatively small and demographically homogeneous, with significant heterogeneity in substance use patterns and methodologies across studies. It is also still unclear how drug dosing and drug interactions, as well as socio-demographic and environmental factors affect outcomes. (Briana Lees et al., 2021)

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