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ROLE OF DRUG MISUSE IN PREGNANT WOMEN CAUSING CONGENITAL ANOMALIES IN CHILDREN

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Abstract
The number of babies born with health problems has grown as a result of drug addiction by women who are fertile and drug exposure during pregnancy. Later in life, neurological and neurodevelopmental impairments may result from prenatal exposure to drugs. There are few relevant studies on the impact of psychoactive substances on the neurodevelopmental state of the fetus. It is now urgently necessary for everyone in the world to comprehend the neurodevelopmental effects of drug exposure during pregnancy. This review's objective is to compile the most recent data and evidence about the effects of drug exposure during pregnancy on neurodevelopment. We used the phrases "drugs," "neurodevelopmental consequences," "prenatal drug exposure," and "pregnancy" to search the PubMed, Scopus, and Google Scholar databases for relevant articles. Upon reviewing the literature on drug exposure during pregnancy, it was discovered that there is evidence to suggest that fetuses and children may have some health problems. The neurodevelopmental effects of many psychoactive drugs include altered brain structure, reduced attention span, Down syndrome, ADHD, imbalances in neurotransmitter levels, autism spectrum disorder, and several structural deficiencies. More research is required to determine how exposure to psychoactive substances during pregnancy affects offspring.

Introduction
A person is considered addicted to drugs when they experience a constellation of negative physiological and behavioral outcomes as a result of chronic, heavy usage of these substances. Addiction is characterized by several symptoms, the most prominent of which are cravings for the substance and subsequent withdrawal symptoms after one stops using the drug (1). Women continue to have the same rate of drug and substance usage as males when it comes to non-medical and recreational use (2). There has been an upsurge in the use and misuse of both legal and illegal drugs among women of childbearing age, coinciding with the overall trend of drug addiction (3). Both the mother and the child are at risk for several medical issues that can arise from drug use during

pregnancy. Adverse medication reactions during prenatal brain development are complex and depend on a wide range of factors. Factors that influence the amount of medication that reaches the fetus's blood and central nervous system (CNS) include the time, size, and length of exposure (4). The effects on embryonic organs and fetal toxicity of drugs vary across diverse routes of administration (oral, smoking, inhalation, and injection) since the quantity of drug absorbed varies along these routes (1, 5). There is evidence between substance use to miscarriage in human studies of pregnant women who use illegal substances (1).

The effects of drug usage on a developing child's nervous system are a complex and multi-faceted problem. Researching the effects of drugs on human embryos while they are still in the womb presents several practical challenges. Mothers who are addicted to drugs frequently utilize a wide range of medications, each with its own unique set of pharmacologic effects (6). It is difficult to research the effects of a single substance on the neurodevelopment of the baby in isolation due to this scenario. The mother's hormones and blood sugar levels are additional variables that impact the neurodevelopment of the infant (7). Research on drug use during pregnancy that relies on self-reports, however, can be biased toward underrepresentation (8).

An increasing number of pregnant women are being exposed to drugs, the exact nature of which varies greatly from country to country (9). Pregnancy is a critical time for fetal brain development. Especially during the first three months of a pregnancy, a lot happens (10). The negative impacts on brain structure and function from early life drug and substance exposure are long-lasting (8). The shape of cortical neurons can be altered by prenatal exposure to addictive chemicals including narcotics. It has been previously documented that medicines have a significant impact on the cerebral cortex. Substance abuse changes the neuronal morphology, synaptic plasticity, and receptor function of many inhibitory and excitatory neurons in the midbrain cortex's marginal system (11). Toxic effects on the CNS during pregnancy and the offspring's behavior are well-documented. Prenatal neurodevelopmental injuries persist throughout fetal till adult childhood central nervous system development, according to experimental and animal research (12). Researchers have a difficult challenge in attempting to understand the link between fetal drug exposure and neurodevelopmental outcomes (13). Confounding variables include the kind and dosage of the medication, environmental conditions, individual genetic profiles, and the length of time between exposure to drugs during pregnancy and the neurodevelopmental effects in offspring. Under these conditions, scientists are unable to establish a causal relationship between prenatal drug exposure and developmental delays in children (12). The effects of certain kinds of drugs on foetal health have been the subject of earlier research. A comprehensive explanation of neurodevelopmental problems is part of the goal of this review, which aims to outline the consequences of various types of drugs consumed by pregnant women on children.

Pregnancy and Drug Kinetics

The dosage of the medication, the pharmacokinetic properties of the mother's pharmaceuticals, and the rate of drug distribution and excretion in the developing fetus are all crucial aspects of fetal drug exposure. The pH gradient across the placenta, Drug lipophilicity, and the drug's protein-binding characteristics are the three primary parameters that govern the pace of drug transfer from the placenta to the fetal body (14). Freely absorbed by the fetal body from the placenta are non-ionized, lipid-soluble, low-molecular-weight medications. The fetal/maternal drug ratio, or concentration gradient, and placental blood flow are two critical components that ensure drug equilibration between the two blood compartments (15).

The fetus is exposed to excessive quantities of medications since its metabolic ability for the metabolism of chemicals and pharmaceuticals given to the mother is not fully developed during the first three months of fetus's life (16). Several pharmacokinetic characteristics, including medication absorption, metabolism, distribution, and excretion, are impacted by physiological changes that occur during pregnancy (17). Because the small intestine drug transit time and stomach emptying time both decrease during pregnancy, the first pharmacokinetic parameter, absorption, reduces as well. During pregnancy, the volume of the mother's plasma increases, sometimes by as much as 50% in the final

trimester, which causes the plasma concentration of medicines to decrease (18). Because of their lipophilic chemical composition, most psychotropic drugs are distributed more widely throughout the body while a woman is pregnant. The pharmacokinetics of psychoactive drugs alter during pregnancy, and hormonal activation or inhibition of metabolic pathways is a major factor in this shift (18, 19).

Cannabis

Cannabis or marijuana, is a hallucinogenic compound most often found in delta-9-tetrahydrocannabinol (THC). Cannabinol (CBN) and cannabidiol (CBD) are two more cannabinoids. "Cannabis" can refer to a variety of cannabinoids derived from the cannabis plant (20). The quickest way for THC to reach the bloodstream is by inhalation of marijuana. Dabbing, vaporization, and smoking are the three main methods for inhaling marijuana. Oral marijuana comes in many forms, including cakes, beverages, tinctures, sweets, snacks, and drops. The oils and waxes that include marijuana are also used to make rectal and vaginal suppositories (21).

The perception that marijuana is safe to use during pregnancy contributes to its high rate of maternal usage, which in turn affects the drug's pharmacokinetics throughout pregnancy (22). Animal and human research have shown that fetal blood concentrations of THC are proportional to maternal blood concentrations and that THC crosses the placenta quickly. Cannabinoids in marijuana alter the normal transport and physiology of the placenta (23). Exposure to cannabidiol (CBD) enhances fetal exposure to other toxins and drugs because it makes the placental barrier more permeable to both legal and illegal substances. Prenatal cannabis exposure decreases blood flow, which is critical for supplying the placenta, according to other human research (24). More than 90% of the THC is absorbed when it is taken orally. But less than 20% of it reaches the bloodstream because of first-pass hepatic metabolism. On the other hand, THC fails to pass through the liver's first-pass metabolism after smoking marijuana, leading to very unpredictable bioavailability. Nevertheless, its concentration decreases as a result of pyrolysis, absorption by cigarette butts, and sidestream smoke (25, 26).

Researchers have observed that nutritional deficiencies and the synergistic effects of multiple drug usage make it difficult to draw firm conclusions on the effects of marijuana use during pregnancy on children and their development (27). Researchers have shown structural alterations in the brain, particularly in the nucleus accumbens, as a result of THC's effects on embryonic brains in both animals and humans (28). Stillbirth, spontaneous preterm birth, and low delivery weight were all strongly linked to marijuana usage in a prior study (29). Screens for tetrahydrocannabinolic acid in umbilical cord homogenate were positive, indicating cannabis usage. Concurrent maternal smoke usage muddied the waters and ruined the outcome (30).

As a recreational medication or to relieve morning sickness and nausea, prenatal marijuana usage is widespread. Issues with brain development are seen in babies whose mothers used cannabis while pregnant. Alterations in reaction time to visual stimuli, trembling, and a high-pitched scream are symptoms of these issues (31). Other significant challenges among school-aged children exposed to cannabis during the perinatal trimester include memory and skill gap concerns (32). When children were tested neurologically and their IQs were estimated, it was found that they had varying degrees of difficulty with visual memory, perception, and language understanding throughout their lives. In addition to extreme impulsivity and hyperactivity, children also struggled with poor sustained attention (33).

Pregnant women who used cannabis had a higher risk of having infants with Down syndrome, cardiovascular problems, abnormalities in the arms and hands, and orofacial clefts, according to research out of Hawaii (34). Another Canadian study found that areas with higher rates of cannabis use had a higher prevalence of congenital abnormalities than other regions (35). A further concern with cannabinoid-induced genotoxicity is the high incidence of certain cancers in children, such as

rhabdomyosarcoma, acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), and neuroblastoma (34).

Opioids

The plant *Papaver somniferum* is the source of the coagulated fluid, which is known as opium. Opium contains a variety of alkaloids that have psychedelic effects (36). Opium is primarily an alkaloid plant that contains morphine papaverine, thebaine, codeine, and noscapine. One semi-synthetic opiate that is produced by acetylating morphine is heroin, also known as diamorphine or diacetylmorphine. The pharmacologic effects of opiates like morphine and heroin are transmitted by the stimulation of opioid receptors. Numerous opioid receptor subtypes exist. The μ (mu) receptors are responsible for the behavioral and analgesic effects among them (37).

Opioid usage has become far more common among women of childbearing age. Opioid exposure during pregnancy can impact neuronal development in a direct manner (11). Infants exposed to opioids show brain abnormalities soon after birth, before environmental confounding variables impact neurodevelopment (38). Brain growth and poor neurodevelopmental outcomes are significant health concerns, in addition to the bad neonatal outcomes (such as early delivery, stillbirth, and lower gestational age) linked to prenatal opiate exposure (39).

Nevertheless, it is important to consider maternal confounding variables, such as cigarette and alcohol consumption during pregnancy, or the use of several drugs during pregnancy, since they might impact neurodevelopmental outcomes. The most common negative consequence of using opioids while pregnant is harm to the developing babies' central and peripheral nervous systems (40). The most notable effects of prenatal opioid exposure on brain development are newborn abstinence syndrome and neural tube abnormalities (11). Opioids create a congenital defect known as incomplete neural tube closure, which occurs during the fourth or fifth week of embryonic neural tube development. Anencephaly, Spina bifida, and encephalocele are some of the symptoms that may be observed (41). Opioids can alter the amount and shape of connections between various brain regions, such as the thalamus, basal ganglia, and cerebellar white matter. The impact of opioids on the developing fetal brain also changes the myelination process in oligodendrocytes (42). Opioid exposure has negative effects on children's social and emotional development, as well as their psychomotor and cognitive abilities, beginning in infancy and continuing throughout preschool (3). Pregnant women who take opioids are more likely to have children with low IQs, delayed language development and abilities, and attention deficit hyperactivity disorder (ADHD). Previous research lends credence to the hypothesis that youngsters exposed to opioids have a greater risk of developing a spectrum of neurodevelopmental abnormalities (43).

Babies delivered to moms who were addicted to opioids and who took methadone also experienced these issues (3). Previous research has shown that compared to unexposed newborns, methadone-exposed infants display a more dysregulated pattern of neurobehavioral abnormalities from birth (43). Methadone has a low molecular weight and is quite lipophilic. It passes the placenta with ease and gets to the embryo. Methadone significantly alters the maturation and function of a child's neurons, according to research in both experimental and animal models. Methadone is known to have harmful effects on neurons during the crucial phases of myelin development (44). According to Stoetzer et al., methadone inhibits movement. Opioids like methadone negatively affect ion channels, which changes the way neurons in a network operate (45). Methadone causes a dose-and stage-dependent disruption of human cerebral organoids' integrity. Methadone inhibits NMDA receptors in organoids derived from human brain cortex as well (7).

It has been proven that exposure to methadone during pregnancy can lead to impaired attention, control, and movement quality. In the long run, babies exposed to methadone have problems with control, intelligence, neurological impairments, symptoms of stress, and abstinence (46). Distinct neurobehavioral profiles, including delayed cognitive and motor development, continue throughout

the first four and a half years of a child's life, according to results of follow-up investigations in children at 24 months of age. On the other hand, when comparing prenatally exposed and unexposed newborns, there was no discernible difference (47).

Stimulants

A class of chemicals known as amphetamine-type stimulants (ATSs) is mostly composed of synthetic compounds. Crystal meth, acme, and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) are the main components. The CNS is stimulated by ATSs because they disrupt the processes that produce norepinephrine, dopamine, and serotonin (48).

Amphetamines and methamphetamines influence levels of neurotransmitters in the brain in several ways. The primary basis for the operation of ATSs is the information sent between neurons and their direct contacts. The exact method by which each given chemical exerts its effects may vary, but the underlying concepts are always the same (49). At synapses between neurons, ATSs raise concentrations of neurotransmitters. As an alternative, ATSs are considered non-catecholamine sympathetic medicines since they lack the molecular structures of catecholamines and have no effect on receptors (1). There is an increase in monoamine concentrations in neuronal cytosols and synapses after methamphetamine reaches the CNS, and it also releases dopamine, noradrenaline, and serotonin. Another way that ATSs raise concentrations of neurotransmitters in synapses between neurons is by inhibiting their reabsorption. One enzyme that contributes to the breakdown and inactivation of monoamines is monoamine oxidase (MAO) (50). A rise in monoamine concentration is the outcome of the inhibition of MAO action by the methyl group on the alpha carbon in the methamphetamine molecule (1). All of these things work together to excite the CNS. Dopaminergic and serotonergic neural response pathways are the primary targets of methamphetamine's effects. Another way of looking at it is that methamphetamine is a drug that is not sympathetic to catecholamines (51).

The pharmacokinetics of methamphetamine reveal that it is extensively absorbed by the intestines. Compared to its less lipophilic equivalents, like amphetamine, it crosses the blood-brain barrier more easily (52). There is a widespread distribution of methamphetamine throughout the body. Its metabolism varies between different kinds of animals. Methamphetamine is eliminated from the body in its unmodified form through urine (53). The hydroxylation process in the liver results in the formation of hydroxymethamphetamine, one of the metabolites of methamphetamine that is eliminated in the urine. Amphetamine, the other metabolite, is formed when methamphetamine is N-demethylated (54).

Dopamine auto-oxidation leads to the generation of very reactive free radicals, which in turn cause the neurotoxic effects of methamphetamine (55). One of the main reasons for dopamine terminal damage is intraneuronal oxidation, which occurs when the vesicular pool storage in dopaminergic neurons is depleted and transferred to the cytoplasmic compartment (56, 57). One key component of methamphetamine's neurotoxic effect is an imbalance in the three pools of dopamine—the vesicular, cytoplasmic, and extracellular varieties. Degradation of dopaminergic receptors, reduction in dopamine production, and emergence of withdrawal symptoms are all outcomes of chronic methamphetamine use (58).

Serotonergic and Dopaminergic pathways link many brain regions that are involved in pleasure, motor control, and addiction (59). Methamphetamine enters neurons by monoamine transporters, which also carry dopamine, serotonin, and norepinephrine. An increase in monoamine release into the synaptic space and displacement of monoamine pools in intracellular and vesicular compartments are both effects of methamphetamine (60).

The neurotoxic drug methamphetamine has the potential to induce terminal degeneration of the striatal nerve. The release of dopamine from intracellular pools into the extracellular environment is what causes methamphetamine to increase dopamine concentrations outside of cells (61). The

neurotoxic effects of methamphetamine are brought about by the auto-oxidation of dopamine, which results in the formation of very reactive free radicals. Dopamine redistribution from vesicular reserves to the cytoplasmic compartment promotes intraneuronal oxidation and, ultimately, dopamine terminal damage(1). The desire to increase the dose is triggered by diminished dopamine synthesis and a loss of dopaminergic receptors in methamphetamine-addicted patients and long-term users (62). Dopamine receptor overactivation mediates methamphetamine-induced hyperthermia. The importance of dopamine begins to diminish with time, though, and serotonin takes center stage. Methamphetamine causes sadness and sleep difficulties by reducing forebrain serotonin concentrations (63).

Compared to males, women are more easily affected by the drug. There has been an alarming uptick in the usage of methamphetamine by pregnant women. A woman's susceptibility to medicines changes significantly during pregnancy. Pregnant women with addiction problems face many risks, including malnutrition and an increased risk of fetal mortality due to increased susceptibility to substances like cocaine [42,43]. Pregnancy-related physiological changes and changes to body water volume impact the biological half-life, distribution volume, concentration peak, and distribution of methamphetamine. The placenta undergoes several changes throughout pregnancy. Use of drugs during pregnancy has significant effects on the placenta's cellular membrane, protein binding, ability to transport nutrients and oxygen, blood flow rate, and fetal drug permeability (1). Methamphetamine is able to quickly cross the placental barrier, according to previous research. Additionally, research has demonstrated that fetal blood circulatory system methamphetamine concentrations are half those of maternal blood concentrations (64). Methamphetamine undergoes most of its metabolism in the liver; however, the developing liver's enzyme system is not yet capable of processing high doses of the substance. High drug concentrations can be detected in fetal plasma after repeated exposure to methamphetamine (65). Prenatal exposure to methamphetamine lowers the embryo's antioxidant levels, which increases the risk of oxidative damage to DNA, lipids, and proteins. This is because methamphetamine is an oxidant and produces reactive oxygen species (66).

An increase in synaptic activity, which leads to neurotoxic effects on the central nervous system, follows a drop in dopamine and noradrenaline levels, as shown in previous research. Researchers shown that the synergistic effects of methamphetamine and monoamine neurotransmitters can disrupt brain development in utero (67).

Impaired brain development is linked to problems with prenatal methamphetamine exposure (68). Poor motor skills, abnormalities in electroencephalogram (EEG) patterns, increased stress levels, and physical tension are some of the neurobehavioral development symptoms observed in infants exposed to methamphetamine during pregnancy (69). Children exposed to methamphetamine had a higher risk of low birth weight, stillbirth, and intrauterine development retardation, according to other research (70). Methamphetamine can potentially impact the anatomy of the fetal brain. Prenatal methamphetamine exposure has been linked to smaller striatums, fewer dopamine (D2) receptors, and lower volumes of subcortical regions such as the putamen caudate nucleus, hippocampus, and, globus pallidus, according to previous research (70, 71). Adverse effects on social adaptation and cognitive development are seen in pre-schoolers and elementary school-aged children who were exposed to methamphetamine during pregnancy. They exhibit symptoms of personality problems including attention deficit hyperactivity disorder (ADHD), emotional instability, anxiety, and hostility (72).

Conclusion

Numerous physiological changes in the body occur during pregnancy, and these changes inevitably affect how drugs are delivered to the developing fetus. Notably, a large number of legal and illegal psychoactive substances are made to cross human barriers like the placenta and the blood-brain barrier to enter the brain and ultimately the fetus's body.

Pregnancy and substance use are linked to a higher incidence of neurodevelopmental problems. During the last stages of fetal development, while the major organs are developing, drugs may have

mild effects. Unusual prenatal development patterns, unbalanced neurotransmitter volume, abnormal brain formation, and changed receptor expression are a few of these detrimental effects. When combined, the results of earlier research point to a strong correlation between drug misuse at birth and subsequent neurodevelopmental problems.

The quantity and timing of drug use during pregnancy, as well as the potential health effects on children, require more investigation.

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