Teratogenic Risks from Exposure to Illicit Drugs

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KEYWORDS

• Addiction • Fetal effects • Illicit drug use • Teratogenic risk
• Pregnancy complications

KEY POINTS

- This article presents issues pertaining to limitations with reports about fetal risks and describes current information in humans about fetal effects for specific illicit drugs.
- Associating illicit drug use with eventual pregnancy outcome is difficult. Concurrent use with multiple substances is frequent, and many users are economically disadvantaged, which contributes to unfavorable perinatal outcomes.
- Teratogenic effects may be manifested not only as an intrauterine demise or dysmorphism, but also as growth restriction or behavioral changes.
- Except for maternal alcohol exposure, no birth defect syndrome has been described for specific illicit substances or prescription drugs of abuse.

INTRODUCTION

Substance use is prevalent in the United States, especially in the reproductive-age population. The 2012 National Survey on Drug Use and Health indicated that 14.7% of the US population aged 12 or older used an illicit drug and 4.9% used prescription-type pain relievers for nonmedical reasons in the past year.[1] Furthermore, 9% of this population had some form of substance use disorder. Cigarette and binge alcohol use (five or more drinks on at least one occasion in past 30 days) involved 24.1% and 23.2% of the population, respectively.

Chronic substance use may affect menstrual cycles and semen analysis, but these effects are generally reversible with discontinuation of the drug.[2–5] For this reason, reproductive-age women with addiction disorders may still conceive at any time. Delivery of a drug or chemical by the sperm to the oocyte may be associated with

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developmental toxicity, although less is understood and toxicity has not been well-demonstrated in humans.

Illicit drugs include cannabis, stimulants, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically. According to the 2012 National Survey on Drug Use and Health, an estimated 4.4% of pregnant women reported illicit drug use in the past 30 days.[1] A second study showed that whereas 0.1% of pregnant women were estimated to have used heroin in the past 30 days, 1% of pregnant women reported nonmedical use of an opioid-containing pain medication.[6] Even though a reduction in substance use may occur during pregnancy, some women may not alter their drug use patterns until at least pregnancy is confirmed. For these reasons, a large number of fetuses are exposed to illicit substances, including during critical stages of organogenesis.

Associating illicit drug use with eventual pregnancy outcome is difficult, because concurrent use of multiple substances is frequent and many users are members of economically disadvantaged segments of society in which unfavorable perinatal outcomes are more common. It is also difficult to follow infant outcomes in such pregnancies and to analyze research data. This article presents issues pertaining to limitations with published investigations about fetal risks and describes the most current information in humans about fetal effects from specific illicit substances (**Table 1**).

LIMITATIONS WITH INVESTIGATIONS ABOUT FETAL RISKS

Difficulties in accurately monitoring dose and exposure of a substance continue to undermine the strength of many observations regarding adverse perinatal effects. Illicit drugs and prescription medications for recreational reasons may be intentionally or inadvertently taken at potentially toxic doses. An accurate evaluation of dosage and the exact period of exposure are often not possible. Addiction or the recreational use of illicit substances may lead to the intake of these drugs in large and uncontrolled doses. For example, when amphetamine use has been studied among addicted mothers, it has been difficult to identify which adverse effects may have resulted from these drugs or the simultaneous use of other substances (eg, ethanol), and poor maternal nutrition, hygiene, and attendance at prenatal visits.

Any illicit drug unbound to proteins can freely pass from the maternal compartment, across the placenta, and into the fetal compartment. Concentrations in the fetal serum can be the same or even higher than in the mother. Little doubt exists that passage of the drug or metabolite into the fetal central nervous system is unimpeded. Effects on the developing embryo and fetus depend on gestational timing, extent of drug distribution, uteroplacental perfusion, and drug or metabolite amount.

Teratogenic effects may be manifested not only as an intrauterine demise or dysmorphism, but also as growth restriction or behavioral changes. Although an association between a substance and an anomaly (eg, midline facial defects) may be suggested with a particular genetic susceptibility, subsequent epidemiologic studies often do not ascribe any substance exposure with an increase in human malformations. It is also not possible to conclude in human beings that heritable birth defects are increased after exposure to a certain drug or chemical.

Small population sizes and unblinded evaluations of drug-exposed newborns raise questions about the significance of any teratogenic observations. Other causes for adverse pregnancy outcome may also exist within drug-abusing populations. Impurity of most illicit drugs and the common practice of using multiple substances either combined or at separate times make it difficult to ascribe specific fetal effects to a certain compound.

Table 1
Suspected effects described in humans after exposure to illicit drugs during pregnancy

Illicit Drug	Effects on Mother/ Pregnancy	Potential Structural Effects	Neurobehavioral Effects
Cannabis	Shorter gestation Lower birth weight	None specific	Impaired executive function
Opioids	Preterm delivery PPROM Meconium-stained amniotic fluid IUGR Chorioamnionitis Fetal death	Congenital heart defects Neural tube defect	Neonatal abstinence syndrome Aggressiveness Impulsiveness Increased temper Poorer self-confidence Impaired memory Impaired perception
Cocaine	Preterm delivery Placental abruption Uterine rupture Fetal death IUGR	Necrotizing enterocolitis Disagreement regarding structural defects	Impaired language development Attention deficits in males Inhibition deficits in males
Amphetamines	Maternal psychiatric diagnosis	Oral clefts Smaller head circumference Shorter length Disagreement regarding other structural defects	Increased emotional reactivity Depression Anxiety ADHD Externalizing behavior Aggressiveness
Hallucinogens	No data	PCP: Microcephaly Abnormal facies Intracranial abnormalities Respiratory anomalies Cardiovascular defects Urinary tract anomalies Musculoskeletal abnormalities LSD: Limb defects Ocular abnormalities MDMA: Congenital heart disease Musculoskeletal abnormalities Peyote: No data	PCP: Attachment disorder LSD: No data MDMA: Impaired motor abilities at 4 mo Peyote: No data
Inhalants	Maternal electrolyte abnormalities Maternal arrhythmias Maternal RTA IUGR Preterm labor	Microcephaly Craniofacial abnormalities similar to those seen in fetal alcohol syndrome	Developmental delay Growth impairment Attention deficits Language deficits Cerebellar dysfunction

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; IUGR, intrauterine growth restriction; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine (ecstasy); PCP, phencyclidine; PPROM, preterm premature rupture of membranes; RTA, renal tubular acidosis.

Besides maternal alcohol, a birth defect syndrome has not been described for illicit substances or prescription drugs of abuse. The broad range of the described defects makes definition of a single syndrome difficult. Many controlled studies have observed an increase in birth defects with certain substances during human pregnancy. The lack of uniformity among the defects, insufficient number of study cases, and failure to use a comparable group of non–drug-using women as control subjects cast doubt on the relative risks. The inconsistency in these retrospective associations, along with criticisms about potential bias in data collection, makes it unjustified to consider a given illicit drug as causing these malformations. It has been recently demonstrated, however, that use of tobacco (including secondhand smoke exposure) or any illicit drug leads to an increased risk of stillbirth.[7]

Measuring the in utero effect of alcohol and substance exposure on infant and child development also presents many challenges. Although animal studies indicate that alcohol and drugs reduce the density of cortical neurons and change dendritic connections, their significance in human development is unclear.[8] Altered fetal behaviors are usually insidious, variable, and not easily recognized. Measureable effects during lengthy periods of development can less precisely implicate a prior drug exposure. Social, cultural, environmental, and genetic factors are influential, so evidence of altered behavior or impaired development in previously exposed children may not only measure teratogenic effects of substances but also parental influences on behavior.

Risks from exposure to illicit drugs during breastfeeding are less of an issue. A substance and its active metabolites enter breast milk in undetermined quantities and are usually absorbed in small amounts by the neonate. Accumulated substances in exposed infants can contribute to poor suckling, irritability, or somnolence. For this reason, repeated use of psychotherapeutic drugs or illicit substances by nursing mothers is not recommended by the American Academy of Pediatrics.[9]

EFFECTS FROM SPECIFIC ILLICIT DRUGS

Cannabis

Marijuana smoke contains many compounds. The most active and most well-studied of these is Δ9-tetrahydrocannabinol, which binds to the cannabinoid receptors of the central nervous system. Intoxication leads to an elevated heart rate, a feeling of euphoria, decreased alertness, decrease in motor stability, congestion, and increased appetite, although the mechanism through which it achieves these is not clear.[10]

Numerous published studies and case reports describe no patterns between maternal cannabis use and malformations. There is an increased incidence of low birth weight among neonates born to mothers who used marijuana during pregnancy.[11] This may relate to smoking marijuana more than five times per week being associated with a slightly shortened gestation by 0.8 weeks.[11,12]

Unlike most other substances of abuse, marijuana has been extensively studied in a longitudinal manner to evaluate long-term neurobehavioral outcomes. The Ottawa Prenatal Prospective study followed a long-term cohort of children exposed in utero to marijuana. In the toddler stage, there was no evidence of impaired growth or behavior. However, after age 3, there are notable differences in executive function (behaviors associated with impulsivity, attention, and problem solving).[13] It is speculated that cannabinoids may differentially impact the developing frontal lobe.

Opioids

Opioids bind to opioid receptors of the central nervous system, leading to a decreased sensation of pain without loss of consciousness, and often accompanied by a feeling

of euphoria. Physiologic effects of these drugs include decreased sympathetic tone and histamine release, which lead to respiratory depression, sedation, decreased gastrointestinal motility, itching, miosis, and urinary retention.[14,15]

Opioid use during pregnancy has been associated with increased complications, such as preterm delivery,[16] preterm premature rupture of membranes, meconium-stained amniotic fluid, intrauterine growth restriction, chorioamnionitis, and perinatal death.[16–18] Fetuses exposed to opioids in utero are more likely than their peers to have any birth defect. A 2011 analysis of data in the National Birth Defects Prevention Study reported statistically significant associations between the use of opioid medications in the interval from 1 month before to 3 months after conception and the following defects: conoventricular septal defects (odds ratio [OR], 2.7; 95% confidence interval [CI], 1.1–6.3), atrioventricular septal defects (OR, 2.0; 95% CI, 1.2–3.6), hypoplastic left heart syndrome (OR, 2.4; 95% CI, 1.4–4.1), spina bifida (OR, 2.0; 95% CI, 1.3–3.2), and gastroschisis (OR, 1.8; 95% CI, 1.1–2.9).[19] The authors noted the limitations of their data, which relied on maternal recall of drugs used and did not take into account dosage or the use of combination products. No specific pattern of birth defects has been identified, however, raising the question as to whether there are confounding variables that were not controlled in those studies.[17,18]

Neonatal abstinence syndrome (NAS) is a well-described sequelae of neonates exposed to opioids in utero. Withdrawal causes autonomic hyperactivity, characterized by fever, irritability, hypertonia, diarrhea, feeding dysfunction, and sleep disturbances.[20] The severity of NAS does not seem to vary with different maternal doses of methadone.[21] More is written about this syndrome and its management elsewhere in this issue.

Methadone and buprenorphine are used as alternatives to heroin or other opioid use to decrease associated high-risk maternal behaviors. These maintenance medications have not been definitively shown to have any greater or lesser effect than heroin on the developing fetus, nor do they prevent NAS. Because of its longer half-life, methadone may cause more severe or prolonged NAS compared with buprenorphine.[22]

Throughout childhood, children chronically exposed to opioids in utero have been shown to have slight differences from their nonexposed peers of similar socioeconomic backgrounds. Exposed children showed increased episodes of temper, impulsiveness, and aggressiveness, and poorer self-confidence.[23] Tests of memory and perception revealed impaired abilities in these realms.[23] Body measurements also revealed lower weight and smaller head circumference.[24]

The American Academy of Pediatrics recommends against the use of heroin or other nonprescription opioids by breastfeeding mothers.[9] This contrasts with mothers maintained on methadone or buprenorphine who are encouraged to breastfeed because this has led to less severe NAS symptoms in multiple studies.[24,25] Opioids are commonly used for pain control after cesarean deliveries and this is not a contraindication to breastfeeding.[9] However, there is a recent case of neonatal death from morphine overdose in a nursing infant whose mother was taking codeine and later found to be a rapid metabolizer of codeine into morphine.[26] This has led the Food and Drug Administration to advise against the use of codeine in nursing mothers, unless the mother is known to not metabolize codeine rapidly.[27]

Cocaine

Cocaine blocks reuptake of catecholamines and serotonin and enhances presynaptic release of these same substances from peripheral nerve terminals. Vasoconstriction and transient hypertension result from systemic sympathetic effects. In the limbic system, there is an increased release of excitatory amino acids glutamate and aspartate.

Cocaine also has a local anesthetic effect because of its blockade of sodium channels.[28] These effects can cause specific problems during pregnancy because this vasoconstriction may lead to decreased placental perfusion.[29]

Cocaine has been linked to several fetal anomalies including craniofacial abnormalities, limb deformities, and urinary tract anomalies. However, more recent analyses shed doubt on those findings. A large, prospective multisite study examining 717 cocaine-exposed pregnancies indicated that structural abnormalities are no higher in cocaine-exposed infants than control subjects.[30]

Fetal growth can be impaired, with an increased incidence of intrauterine growth restriction among these fetuses.[30,31] Longitudinal studies have revealed that these children do tend to catch up to a normal weight range by 6.5 and 13 months of life, although they may be slightly shorter than their peers. It is unclear whether this short stature is caused by cocaine or a confounder more likely caused by concomitant alcohol use.[32]

Pregnancies exposed to cocaine have an increased incidence of preterm delivery[31] and placental abruption[33]; cases of uterine rupture[34] and fetal death[35] associated with maternal cocaine use also have been reported. Necrotizing enterocolitis seems to be increased among neonates exposed to cocaine in utero.[36] There is disagreement regarding whether the rate of sudden infant death syndrome is also increased. A meta-analysis concluded that there is an increased risk of sudden infant death syndrome in any infant exposed to drugs in utero, but no increased risk was found specifically for cocaine use alone.[37]

Cocaine also affects fetal and postnatal behavior. Symptoms of acute fetal intoxication and withdrawal have been observed sonographically.[38] With chronic use, ultrasound findings of abnormal fetal behavioral state organization and regulation were viewed, which correlated with similar abnormal behaviors viewed in the neonatal period.[38] After birth, language development is impaired.[39] Males (but not females) exposed to cocaine have been shown to have deficits with attention and inhibition.[40]

Amphetamines

Amphetamines act as indirect sympathomimetics by increasing the concentration of catecholamines at the postsynaptic terminal through blockade of reuptake (similar to cocaine), and increasing release of dopamine and norepinephrine. These lead to systemic sympathetic effects, such as increased heart rate, cardiac output, and blood pressure; dilated pupils; and bronchodilation.[41]

Retrospective studies and case reports have suggested that methamphetamine use is associated with pregnancy complications, such as hypertensive disease, postpartum hemorrhage, and retained placenta. However, a more recent prospective study seems to disprove these findings, revealing an absence of serious maternal complications with the exception of maternal psychiatric disorders.[42] Case reports have linked maternal amphetamine use with congenital heart disease, biliary atresia, and gastroschisis. A prospective study did not confirm any of these associations, however, but did find an increased incidence of oral clefts.[43] Infants exposed to methamphetamines do have a smaller head circumference and shorter length than their peers.[42] Neonates exposed to amphetamines in utero exhibited poor suck, increased jitteriness, and autonomic stress, and were more likely to be admitted to the neonatal intensive care unit after birth.[42]

Throughout childhood, these children often suffer from several behavioral and developmental issues. However, these do not seem directly the result of methamphetamine exposure. A study that compared methamphetamine-exposed children raised in normal versus high-risk environments found that neurobehavioral deficits in these children at 3 years of age could be attributed to their environment.[44] When data from these same study subjects were examined at both 3 and 5 years of age and

compared with control subjects, significant deficits were noted. There was an increase in emotional reactivity and anxiety and depression at both 3 and 5 years. At 5 years only, an increase in attention-deficit/hyperactivity disorder was noted, as was an increase in externalizing and aggressive behavior. These findings were more marked for boys than girls, and were also more severe in the offspring of mothers with heavy methamphetamine use, defined as more than three times per week.[45]

Hallucinogens

Hallucinogens are a diverse class of compounds. The pharmacology of these substances is quite varied, but all seem to act through serotonin pathways in the central nervous system.[46] Of these multiple compounds, the most commonly abused are phencyclidine, lysergic acid diethylamide (LSD), and 3,4-methylenedioxymethamphetamine (MDMA, commonly known as "ecstasy"). Native Americans are known to smoke buttons from the peyote cactus in religious ceremonies.[47] The active substance in peyote is mescaline, which is also a hallucinogen.

Literature evaluating the outcomes of fetuses exposed to hallucinogens is sparse. Nearly all reported experiences are published cases and, thus, quite limited. Phencyclidine use has been linked to birth defects, such as microcephaly[48] and abnormal facies.[49] Another case report found significant intracranial abnormalities and defects of the cardiovascular, respiratory, urinary, and musculoskeletal systems with subsequent neonatal death.[50] After delivery, these infants may display increased tone and jitteriness, and lethargy.[49] Sleep disturbances and abnormal temperament have also been described.[51] Through the first year of life, an attachment disorder was described, but there is no evidence of other behavioral deficits.[51]

Case reports exist of prenatal LSD exposure leading to defects, such as limb defects and eye abnormalities.[52,53] There are no published studies or case reports evaluating neurobehavioral outcomes in children exposed to LSD in utero.

There are limited data regarding MDMA ("ecstasy") use in pregnancy. One study demonstrated an increased risk of birth defects, most notably congenital heart disease and musculoskeletal abnormalities.[54] Another study of infants exposed to MDMA in utero described impaired motor abilities at 4 months but no other neurobehavioral defecits.[55]

There are no data regarding the effects of peyote use on human pregnancies.

Inhalants

Inhalants represent a diverse group of compounds that are inhaled to achieve intoxicating properties. These include solvents, such as toluene; fuels; anesthetics; nitrous oxide; and alkyl nitrites. Although these substances differ significantly, their pharmacologic and behavioral effects are quite similar and the effect is to produce an alcohol-like intoxication, characterized by euphoria, slurred speech, dizziness, incoordination, involuntary eye movement, slowed thinking, and lethargy.[56,57] The mechanism by which these physiologic effects is achieved is unknown. Although some may be exposed to these compounds in the workplace, concentrations to which abusers are exposed are approximately 50 times greater than the maximum allowed in the workplace.[58] Toluene is the most well-studied of these compounds and is found in many glues and other industrial chemicals that are abused as inhalants.

Medical complications seen in abusers of these substances include electrolyte disturbances, cardiac arrhythmias, and renal tubular acidosis.[59] Pregnancy is often complicated by preterm labor and intrauterine growth restriction; in one study of toluene-exposed pregnancies, these were observed in 42% and 52% of cases, respectively.[60]

Many structural defects have been noted in fetuses exposed to inhalants. Toluene has risk of microcephaly as high as 32% to 33%.[60,61] Also observed are other craniofacial abnormalities similar to those seen in fetal alcohol syndrome: narrow bifrontal diameter, hypoplastic midface, short palpebral fissures, wide nasal bridge, blunt fingertips, and abnormal palmar creases; these have been commonly seen in infants exposed to inhalants in the absence of alcohol exposure.[60]

Unfortunately, children exposed to toluene in utero exhibit significant long-term functional and neurobehavioral deficits. One report indicated that as many as 38% of affected children have some developmental delay.[60] Microcephaly is common. Overall growth can be impaired[60] even after birth as described in six of eight toluene-exposed children who were born with a normal head circumference.[61] Attention and language deficits are common.[59] Central nervous system impairment, including cerebellar dysfunction, has also been noted.[59]

SUMMARY

Pregnant women including those with addictive disorders are commonly concerned about health issues affecting their unborn babies and themselves. Counseling about harmful effects from in utero exposure to a specific illicit or prescription drug is often limited and with usually no defined congenital anomalies or long-term behavior patterns. Fetal ultrasound imaging for anatomy and growth is essential early and repeatedly during pregnancy, although most infants appear healthy at birth and appropriately sized with no birth defects. Many women with a recent history of substance abuse seek prenatal care but do not desire specialized clinics for addiction. Benefits from attending such specialized settings can be offset by difficulty with accessibility. Comprehensive care by qualified practitioners and treatment of alcohol and other drug addictions remain essential for women on the road to recovery and the welfare of their fetus. Regardless of the site of prenatal care, long-term provision of services (nutrition, counseling, social) is vital to fetal and newborn well-being. Continuity of care requires collaboration and cooperation among many community-based services, ranging from agencies that offer safe housing and programs that stress parenting education; encourage responsible breastfeeding; and address issues of domestic violence, abuse, and victimization. With the help of family and peers, these services give the mother the best chance of providing a drug-free environment for growth and development of their fetus or newborn infant. Furthermore, nonpunitive services can better identify and reduce behaviors in mothers whose attention to the infant and other children is reduced, thereby possibly improving on their child's development.

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