Anesthetic Implications of Drug Abuse in Pregnancy

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Substance abuse has crossed social, economic, and geographic borders and—throughout the world—remains one of the major problems facing society today. The prevalence of substance abuse in young adults (including women) has increased markedly over the past 20 years. Nearly 90% of drug-abusing women are of childbearing age. Consequently, it is not unusual to encounter pregnant women who abuse illicit drugs, as numerous case reports of drug abuse in pregnancy confirm. The diverse clinical manifestations of drug abuse combined with physiologic changes of pregnancy, and pathophysiology of coexisting pregnancy-related disease may lead to life-threatening complications and significantly impact the practice of obstetrical anesthesia. Regardless of the drug(s) ingested and clinical manifestations, it is always difficult to predict the exact anesthetic implications in chemically dependent patients.

Keywords: Amphetamines; anesthesia, obstetrical; caffeine; chemical dependency; cocaine; drug abuse; drug addiction; ethanol; hallucinogens; marijuana; opioids; pregnancy; solvents; substance abuse; tobacco.

Introduction

Substance abuse is described as "self-administration of various drugs that deviate from medically or socially accepted use, which, if prolonged, can lead to the development of physical and psychological dependence."1 This disease process, often referred to as chemical dependency, is characterized by periodic or continuous impaired control over drug(s) intake (despite awareness of adverse consequences), preoccupation with drug(s) acquisition, and distortions of mental capacity, most notably denial.2 Psychological personality characteristics seem to predispose to, rather than result from, drug addiction.1,2 Most often abuse of an illicit substance is first suspected or diagnosed during medical management of another condition such as hepatitis, human immunodeficiency syndrome (HIV), or pregnancy.1 Regardless of the drug(s) ingested and clinical manifestations present, it is always difficult to predict the exact anesthetic implications in chemically dependent patients.

Substance abuse has crossed social, economic, and geographic borders, and it remains one of the major problems facing society today.3 The prevalence of recreational drug abuse among young adults (including women) has increased markedly over the past two decades.4,5 Approximately 250,000 women in the United States meet the criteria for intravenous (IV) drug abuse. Nearly 90% of these women are of childbearing age.6,7 Consequently, it is not surprising to find parturients who abuse drugs, to which numerous reports of drug abuse in pregnancy attest.8-11 The diverse clinical manifestations of maternal drug
addiction may result in life-threatening complications and significantly impact the practice of obstetric anesthesia. Anesthesiologists become involved in the care of drug-abusing parturients either in emergency situations, such as fetal distress, placental abruption, or uterine rupture, or in more controlled situations, such as when labor analgesia is requested.

Illicit substances most commonly abused in pregnancy include cocaine, amphetamines, opioids, ethanol, tobacco, marijuana, caffeine, and toluene-based solvents. Polysubstance abuse is very common.21 Most parturients with a history of drug abuse deny the fact when they are interviewed preoperatively by anesthesiologists or obstetricians.2,15 A high index of suspicion for drug abuse in pregnancy, combined with nonjudgmental questioning of every parturient, is therefore necessary. Risk factors suggesting substance abuse in pregnancy include lack of prenatal care, history of premature labor, and cigarette smoking.14,15 The American College of Obstetricians and Gynecologists (ACOG) has made several recommendations regarding management of parturients with drug abuse during pregnancy.16 Women who acknowledge use of illicit substance during pregnancy should be counseled and offered necessary treatment. ACOG also has acknowledged that some states consider intrauterine fetal drug exposure to be a form of child neglect or abuse under the law.16

Cocaine

Epidemiology and Pathophysiology

Five million Americans are regular users of cocaine, 6,000 use the drug for the first time each day, and more than 30 million have tried cocaine at least once.12 Cocaine is an alkaloid (benzoylmethylecgonine, C17H21NO4) that is prepared from the leaves of Erythroxylon coca plant, indigenous to Peru, Ecuador, and Bolivia.17 The drug was first introduced to modern medicine as a local anesthetic in 1884.18 Cocaine hydrochloride, the common pharmaceutical form, is prepared by dissolving the alkaloid in hydrochloric acid to form a water-soluble salt, which has topical anesthetic properties. It is commercially available in a hydrochloride form as white powder, granules, or crystals. The hydrochloride form of cocaine undergoes heat degradation and, therefore, cannot be smoked for recreational purposes. “Crack” is an almost pure cocaine obtained by converting the hydrochloride form back into the alkalized form, an action that is easily accomplished by adding baking soda and water to the cocaine powder. Today, this alkalized form of cocaine is widely smoked throughout the world.19

Cocaine produces prolonged adrenergic stimulation by blocking the presynaptic uptake of sympathetic neurotransmitters including norepinephrine, serotonin, and dopamine.20,21 The euphoric effects of cocaine also result from prolongation of dopamine’s activity in the limbic system and the cerebral cortex.22,23 Smoking the “freebase” (street name for the alkalized form of cocaine) results in very effective transmucosal absorption and high concentrations of plasma cocaine. The use of cocaine rapidly leads to physical dependence. Sudden discontinuation of cocaine intake results in fatigue, mental depression, and craving for the drug. Cocaine is metabolized by the plasma cholinesterases to water-soluble metabolites that are excreted in urine.

Diagnosis and Clinical Presentation

Hypertension, tachycardia, malignant arrhythmias, myocardial ischemia, and myocardial infarction (MI) are all life-threatening cardiovascular complications of catecholamine accumulation following acute cocaine intake.24-29 Mechanisms of cocaine-induced myocardial ischemia and/or MI include thrombosis, vasospasm, or both, and direct myocardial depression.24,27,30 Cocaine-induced cardiovascular complications do not seem to be dose-dependent, and even small recreational doses can lead to significant mortality and morbidity in an otherwise healthy parturient. Pregnancy is associated with increased sensitivity of cardiovascular system to cocaine.25 Identification of cocaine abuse in the parturient presents a significant diagnostic challenge. Lack of prenatal care may suggest the possibility of cocaine or other drug abuse. Patient denial is a common response to direct questioning regarding drug abuse in pregnancy.31 Only 20% of physicians inquire about substance abuse when interviewing their patients.32 In addition to cardiovascular symptoms (hypertension, tachycardia, arrhythmias), other symptoms of cocaine abuse include seizures, hyperreflexia, fever, dilated pupils, emotional instability, proteinuria, and edema. The combination of hypertension, proteinuria, and convulsions resulting from acute cocaine intake may be mistaken for eclampsia (a pregnancy-specific disorder) at presentation; consequently, routine laboratory studies (liver and kidney function tests) may be the key differentials between the two disorders.33 The differential diagnosis is usually aided by maternal urine toxicology screening. A rapid latex agglutination test detecting cocaine metabolites in urine within a few minutes has been developed.34 Cocaine metabolites may be detected in maternal urine for 24 to 60 hours after administration of the drug, depending on the cholinesterase activity.35 Analysis of fetal urine may also serve as a marker of cocaine abuse in pregnancy. Metabolites of cocaine can be found in fetal urine 72 to 96 hours after maternal drug ingestion. Other methods for detection of suspected cocaine abuse in pregnancy include maternal hair and fetal meconium analysis.36-38

Interaction with Pregnancy

The cardiovascular toxicity of cocaine is significantly increased in pregnancy.39 Maternal complications of cocaine ingestion include premature labor, placental abruption, uterine rupture, cardiac dysrhythmias, hepatic rupture, cerebral ischemia/infarction, and death.40-46 Cocaine is rapidly transferred across the placenta to the fetus by simple diffusion, and it may cause significant vasoconstriction by directly affecting fetal blood vessels.47 Indirect
fetal effects of cocaine result from maternal vasoconstriction. Because uterine blood flow is not autoregulated, decreased uteroplacental blood flow may lead to uteroplacental insufficiency, fetal hypoxia, and acidosis. A four-fold increase in fetal distress syndrome leading to abdominal delivery has been reported in parturients who abuse cocaine in the third trimester of pregnancy. The risk of preterm delivery is also increased fourfold in these parturients. Cocaine use in pregnancy leads to subtle molecular effects and may be encountered. Periodic urine testing should be considered in parturients who admit to cocaine abuse.

According to the Committee Opinion published by ACOG, at the time of their first prenatal visit all parturients should be asked about drug use and warned about the dangers of doing so. Periodic urine testing should be considered in parturients who admit to cocaine abuse. Toxicology screening should be performed in suspicious situations such as unexplained fetal intrauterine growth retardation (IUGR). Women with cocaine addiction should be counseled and treated.

**Anesthetic Implications**

Both regional and general anesthesia in the cocaine-abusing parturient may be associated with serious complications. When regional anesthesia is used, combative behavior, altered pain perception, cocaine-induced thrombocytopenia, and ephedrine-resistant hypotension may be encountered. Low doses of phenylephrine titrated to the effect usually restore blood pressure (BP) to normal values. Pronounced abnormalities in endorphin levels and changes in both mu and kappa opioid receptor densities resulting from cocaine addiction may result in perception of pain despite adequate spinal-epidural anesthesia sensory levels.

Hypertension, cardiac arrhythmias, and myocardial ischemia may be encountered during general anesthesia. Propranolol is contraindicated in cocaine-intoxicated parturients because of the potential for unopposed β-adrenergic stimulation following beta blockade. Additionally, propranolol undergoes transplacental transfer and may cause fetal bradycardia. Although esmolol may provide effective control of tachycardia and hypertension, beta-blockade also has been shown to enhance cocaine-induced coronary vasoconstriction. The short elimination half-life of esmolol may offer some advantages if drug administration is deemed necessary.

The administration of hydralazine has recently become a standard drug therapy for the treatment of hypertension in cocaine-addicted parturients. The mechanism of this drug action includes vasodilation and a decrease in systemic vascular resistance (SVR), leading to reflex tachycardia, which may not always be desirable in the patient who is already tachycardic from cocaine intake. Labetalol, a combined nonselective beta and β-adrenergic blocker, rapidly restores BP without affecting heart rate (HR) or uterine blood flow, and it has been recommended for use in cocaine-intoxicated patients. At the University of California, San Diego, we treat severe hypertension secondary to recent cocaine intake by giving labetalol plus nitroglycerine before the induction of general anesthesia. However, Hollander has suggested that labetalol should not be used to treat cocaine-induced hypertension because labetalol’s antagonism of β-adrenergic receptors is greater than its effect on α-adrenergic receptors. The use of calcium channel blockers in drug-abusing parturients remains unclear. Although studies of calcium channel blockers are still ongoing, early evidence suggests that they may not be effective in prevention or treatment of cocaine toxicity. Many other therapeutic agents such as nitroglycerin and nitroprusside have been recommended, although the optimal drug intervention still remains to be established.

All potent volatile anesthetic drugs may produce cardiac arrhythmias and increased SVR in cocaine-intoxicated parturients. Halothane has been found to sensitize the myocardium to the effects of catecholamines and, therefore, it should be avoided in these patients. In sharp contrast to other anesthetic drugs, ketamine, which is a structural analogue of phencyclidine, increases BP, HR, and cardiac output (CO). These indirect cardiovascular effects are due to central stimulation of the sympathetic nervous system. When ketamine is used in cocaine-abusing patients, caution is indicated, because the stimulatory effects of this drug on the central nervous system (CNS) may potentiate the cardiac effects of cocaine by further increasing cocaine-induced elevation in catecholamine levels.

Nitroglycerin is safe and effective for use in the treatment of chest pain secondary to acute cocaine ingestion. Esmolol may have a disinhibitory effect on those portions of the CNS that control extrapyramidal activity. This disinhibition is responsible for a 30% to 60% incidence of myoclonus. Because symptoms of cocaine intake also include myoclonus, seizures, and hyperreflexia, etomidate administration should be undertaken with caution. In contrast, administration of propofol and thiopental sodium for induction of anesthesia in cocaine-abusing parturients seems safe and effective.

Treatment of cocaine addiction with cocaine-specific vaccines is currently under investigation. Binding of antibodies included in the vaccine to cocaine in plasma may prevent the drug’s entry into the CNS. Despite promising initial results, further investigations on the efficacy of cocaine vaccines in cocaine addiction are necessary.

**Amphetamines**

**Epidemiology and Pathophysiology**

Amphetamines are a group of non–catecholamine, indirect-acting sympathomimetic drugs that produce powerful CNS stimulation with peripheral α- and β-adrenergic receptor actions. Structurally, amphetamines closely resemble norepinephrine. The presence of hydroxyl groups in positions 3 and 4 on the benzene ring, and a methylated alpha carbon, interferes with metabolism of
Anesthetic Implications

Animal and human studies have demonstrated an adverse pregnancy outcome with prenatal exposure to amphetamines. Cardiac anomalies, cleft lip and palate, biliary atresia, fetal IUGR, intrauterine fetal demise, and cerebral hemorrhage have been reported. Amphetamines have been associated with obstetrical emergencies such as “fetal distress” and placental abruption. Coexistence of seizures, proteinuria, and hypertension secondary to amphetamine (and cocaine) use has been mistaken for eclampsia. Fetal and neonatal deaths associated with maternal methamphetamine ingestion have been documented.

Anesthetic Implications

The effect of amphetamines on the CNS may have significant anesthetic implications. Fetal distress, abortion of placenta, and other obstetrical emergencies secondary to amphetamine abuse may necessitate emergent cesarean section. Regional anesthesia may be selected, but sympathectomy caused by neuraxial blocks may precipitate severe hypotension. The response to treatment of hypotension with vaspressors is unpredictable in amphetamine-abusing parturients. Psychedelic effects of methylene-dioxymethamphetamine may affect patient behavior and interfere with safe or easy placement of neuraxial blocks.

If general anesthesia is selected, avoidance of halothane is recommended since it may sensitize the myocardium to endogenous catecholamines. Acute intake of amphetamines increases the minimum alveolar concentration (MAC) of potent inhaled anesthetics. In contrast, chronic ingestion decreases the dose requirement for general anesthetic. Adverse cardiovascular effects including cardiac arrest in amphetamine-dependent patients undergoing operative delivery during both regional and general anesthesia have been reported.

Opioids

Epidemiology and Pathophysiology

Addiction to opioids is possible in less than 10 to 14 days, if the drug is administered daily in an increasing dosage. Contrary to common belief, opioid dependence seldom develops from the medical use of these drugs. Opioids may be abused orally, subcutaneously, or intravenously for their analgesic or euphoric properties, or both. Numerous medical problems are encountered in opioid-abusing parturients, particularly with IV drug administration.

Diagnosis and Clinical Presentation

Opioid abuse and addiction in pregnant women have multiple implications for the mother and her fetus. Numerous medical complications such as cellulitis, superficial skin abscesses, septic thrombophlebitis, hepatitis, autoimmune deficiency syndrome (AIDS), endocarditis, and malnutrition have been encountered in parturients who are addicted to opioids. Abuse of other substances, the presence of hepatitis, HIV infection, and absence of prenatal care are all highly suggestive for the diagnosis of opioid dependency in pregnancy. In general, the diagnosis of IV opioid abuse is easier than the diagnosis of cocaine abuse.

Opioid-abusing women may present with symptoms of opioid overdose or acute opioid withdrawal. Clinical manifestations of opioid overdose include slow respiratory rate (RR) with increased tidal volume (VT); however, the increase in VT may not always be present. The pupils are characteristically miotic, although mydriasis has been reported. Acute opioid withdrawal syndrome is manifested by symptoms of increased sympathetic nervous system activity (restlessness, insomnia, mydriasis, tachycardia, tachypnea, and hypertension). Central nervous system manifestations range from dysphoria to various forms of bizarre behavior and unconsciousness. Craving for the drug is associated with lacrimation, rhinorrhea, yawning, and piloerection (“going cold turkey”). The ability to

Diagnosis and Clinical Presentation

Amphetamines stimulate the release of catecholamines from presynaptic vesicles, resulting in euphoria, increased cortical alertness, decreased fatigue, and appetite suppression. The symptoms of acute amphetamine intoxication are clinically indistinguishable from those caused by cocaine. Hypertension, arrhythmias, tachycardia, dilated pupils, hyperreflexia, proteinuria, and confusion all have been reported. Profound thermoregulation disturbances (heat stroke) leading to death may result from MDMA intake. Tolerance is rapidly developed for the euphoric effects of amphetamines, but not for their toxic effects. Symptoms of amphetamine withdrawal also resemble those produced by withdrawal from cocaine.

Cigarette smoking, absence of prenatal care, HIV infection, and IUGR are predictors of amphetamine addiction. Chronic abuse of amphetamines results in depletion of body stores of catecholamines, which may be manifested as anxiety, somnolence, or psychotic state. The treatment of oral amphetamine overdose includes induced emesis and gastric lavage, usually followed by the administration of activated charcoal. Diazepam may be useful in the control of amphetamine-induced seizures. Phenothiazines antagonize amphetamine-related effects on the CNS.

Interaction with Pregnancy

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Anesthetic Implications

The effect of amphetamines on the CNS may have significant anesthetic implications. Fetal distress, abortion of placenta, and other obstetrical emergencies secondary to amphetamines, resulting in their prolonged activity. Amphetamines are abused individually or in conjunction with other CNS stimulants such as opioids or cocaine. Amphetamines are usually abused po or, in the case of methamphetamine, IV. An IV dose causes an immediate effect. Symptoms of amphetamine withdrawal also resemble those produced by withdrawal from cocaine. Crystal methamphetamine (“blue ice”) is a form of the drug that can be smoked. MDMA (3,4 methylene-deoxymethamphetamine) is an analog of methamphetamine that shares several pharmacologic properties with amphetamines and hallucinogenic drugs. MDMA intake. Tolerance is rapidly developed for the euphoric effects of amphetamines, but not for their toxic effects. Symptoms of amphetamine withdrawal also resemble those produced by withdrawal from cocaine.

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of regional anesthesia. HIV is a neurotropic virus and women who abuse opioids does not contraindicate the use of opioids. Although methadone administration is not risk-free, methadone maintenance poses fewer hazards to the mother and fetus than does continued use of IV diamorphine.

**Anesthetic Implications**

To prevent acute withdrawal syndrome, an opioid addict should receive opioid replacement (methadone) throughout labor. Administration of opioid antagonists or agonist-antagonists must be avoided in these patients since they can precipitate acute withdrawal syndrome. Opioid withdrawal syndrome usually develops within minutes after naloxone administration. The symptoms of withdrawal from opioids may be treated with clonidine, diphenhydramine, or doxepin. Clonidine attenuates opioid withdrawal symptoms by replacing opioid-mediated inhibition with α-2 agonist-mediated inhibition of the CNS. It is possible to reverse the withdrawal syndrome by reintroducing the abused opioid or by substituting methadone.

Regional anesthesia may be safely administered to opioid-addicted parturients. However, increased tendency for hypotension should be anticipated following the induction of spinal or epidural anesthesia. Increased incidence of spinal, epidural, and disc space infection have been reported in these patients, irrespective of the type of anesthesia used. Asymptomatic infection with HIV in women who abuse opioids does not contraindicate the use of regional anesthesia. HIV is a neurotropic virus and the CNS is infected early in the course of the disease process. Neurotropic predisposition of an HIV virus is responsible for clinical evidence of neurologic dysfunction at the time of diagnosis of AIDS in up to 30% to 40% of infected patients.

However, regional anesthesia may be relatively contraindicated in AIDS patients with CNS HIV infection and progressive demyelination. Hemodynamic instability, coagulopathy, or sepsis may require administration of general anesthesia in an opioid-addicted parturient. Reduced intravascular fluid volume, malnutrition, or liver disease may require appropriate dose adjustments of anesthetic drugs. Acute administration of opioids decreases anesthetic requirements (decreased MAC). Opioid overdose may cause respiratory depression and loss of the airway. Peripheral IV access can be difficult and central venous access may be required. Chronic opioid use leads to cross-tolerance to other CNS depressants, including anesthetic drugs. Postoperatively, the opioid-abusing parturient often seems to experience an exaggerated degree of pain. Cross-tolerance usually results from chronic receptor stimulation, and decreased pain tolerance is secondary to decreased production of endogenous opioid peptides. Because methadone has minimal analgesic activity, continuous epidural analgesia with local anesthetics and opioids may be advantageous.

**Hallucinogens**

**Epidemiology and Pathophysiology**

Hallucinogens are represented by lysergic acid diethylamide (LSD), phencyclidine (PCP), psilocybin, and mescaline. These drugs are usually ingested orally leading to visual, auditory, and tactile hallucinations, with distortion of surroundings and body image. Although there is a high incidence of psychological dependence, there appears to be no evidence of physical dependence or withdrawal symptoms when hallucinogens are discontinued acutely.

**Diagnosis and Clinical Presentation**

Ingestion of these drugs activates the sympathetic nervous system as evidenced by increased body temperature, tachycardia, hypertension, and dilated pupils. The effects of acute drug intake usually develop over 1 to 2 hours and last for approximately 12 hours. Psychological characteristics of intoxication include anxiety, panic attacks, hallucinations, and fear of “going crazy.” Overdose of hallucinogens has not been associated with mortality, although unrecognized injuries occurring in acute intoxication may reflect the intrinsic analgesic (α2 agonist) properties of these hallucinogenic drugs. On rare occasions, LSD has been reported to cause seizures and apnea. Chronic hallucinogen use is uncommon.

**Interaction with Pregnancy**

Prenatal exposure to PCP is associated with a high incidence of fetal IUGR (32%), preterm labor and delivery (43%), meconium-stained amniotic fluid (30%), and neonatal withdrawal syndrome (27%). Phencyclidine-exposed neonates are often born prematurely. The hallucinogen-induced hyperthermia may increase fetal and maternal oxygen consumption, with possible fetal heat-induced neurologic injury.

**Anesthetic Implications**

It has been reported that anesthesia and surgery may precipitate panic response in hallucinogen-abusing patients. Exaggerated response to sympathomimetic drugs should be anticipated in these parturients. Additionally, hallucinogens may prolong the analgesic and ventilatory...
depressants effects of opioids. Presumed inhibition of plasma cholinesterase activity by LSD and PCP seems to have little clinical significance; however, prolongation of succinylcholine effects is possible. If regional anesthesia is selected for these patients, exercising caution with the use of ephedrine (which has both direct and indirect actions) for the treatment of sympathectomy-induced hypotension is indicated.

Solvent Abuse

**Epidemiology and Pathophysiology**

In 1993, an estimated 900,000 people, of whom 68% were young adults, abused inhalants. Inhalants include a chemically diversified group of substances such as organic solvents and volatile agents that affect the CNS. Toluene is a commonly used industrial solvent and a major component of many household paints and cleaning agents. Solvents may be sniffed from soaked rags, bags, or open containers, as well as ingested orally.

**Diagnosis and Clinical Presentation**

Solvent inhalation causes intense CNS stimulation and disinhibition similar to alcohol ingestion. Toluene sniffing may lead to autonomic cardiac dysfunction, ventricular fibrillation, and MI. Glue sniffing can cause a unique distal and proximal tubular acidosis. Chronic exposure to toluene vapors has been reported to cause changes in the CNS such as diffuse brain atrophy and cerebellar degeneration. Increased airway resistance, pulmonary hypertension, acute respiratory distress syndrome (ARDS), and liver toxicity have all been reported in pregnancy with documented exposure to solvents.

**Interaction with Pregnancy**

Toluene sniffing for recreational purposes in pregnancy has been associated with increased incidence of IUGR, preterm delivery, and prenatal mortality. Although in 1985, Hersh raised the possibility of toluene embryopathy and fetal solvent syndrome, the evidence was inconclusive and the fetal solvent syndrome was never defined. Toluene may augment the manifestations of fetal alcohol syndrome in parturients abusing both substances simultaneously.

**Anesthetic Implications**

Optimal anesthetic management of solvent-abusing parturients requires a high level of suspicion and early diagnosis. Altered perception of sensory stimuli, loss of coordination, headache, nausea, vomiting, and respiratory compromise may result from vapor sniffing. Careful physical examination, including determination of possible sensory or motor deficits, is indicated before induction of labor analgesia or surgical anesthesia for abdominal delivery.

Marijuana

**Epidemiology and Pathophysiology**

Marijuana is a naturally occurring substance that is obtained from the plant Cannabis sativa. The use of marijuana for both medical and recreational indications dates back thousands of years. More than 61 chemicals known as cannabinoids obtained from the Cannabis sativa plant have been identified. Marijuana remains the most commonly used illicit drug among women of childbearing age. It has been estimated that marijuana is used by 9.5% to 27% of parturients. Marijuana is smoked for its hallucinogenic properties. Among all 61 known cannabinoids, delta 9-tetrahydrocannabinol (THC) appears to be the most potent psychoactive agent and of the greatest importance in the recreational use of cannabis.

**Diagnosis and Clinical Presentation**

It is believed that approximately 50% of the THC and other cannabinoids present in a cannabis cigarette are inhaled and enter the bloodstream. High fat solubility of cannabinoids leads to rapid accumulation in adipose tissue from which they are slowly released into the brain. The plasma elimination half-life of cannabinoids in occasional users is approximately 56 hours, whereas in chronic users it is only 28 hours. However, adipose tissue sequestration may extend the tissue half-life to approximately 7 days. It has been reported that complete elimination of a single dose may require up to 30 days. Cannabinoids undergo metabolism in the liver forming more than 20 metabolites, most of which have psychoactive properties.

The effects of acute marijuana use include euphoria, tachycardia, conjunctival congestion, and anxiety. Every body system is affected, although acute toxicity of cannabis is very rare. Pharmacologic actions of marijuana are complex and include a unique blend of effects of alcohol, opioids, tranquilizers, and hallucinogens. Therefore, the clinical picture can be very unpredictable and diagnosis often difficult. A high level of suspicion is necessary.

**Interaction with Pregnancy**

The active ingredient in marijuana, THC, freely crosses the placental barrier and directly affects the fetus. Because most marijuana-addicted parturients also abuse other substances such as tobacco, cocaine, and alcohol, it is difficult to identify the specific effects of cannabis on the fetus. It appears that chronic use of marijuana results in decreased uteroplacental perfusion and IUGR. Chronic use of marijuana may alter pituitary-adrenal axis and hormone production with adverse effects on fertility and pregnancy. Suppression of ovulation has been reported in association with chronic cannabis smoking. Placental production of both estrogen and progesterone may also be altered. There is some evidence that chronic cannabis use may be associated with functional brain changes and subtle impairment in cognitive function.

**References**

1. [Specific reference numbers are not provided in the text.]

The effects of chronic cannabis exposure result in significant changes in the respiratory system, which include bronchitis, squamous metaplasia, and emphysema. Smoke from cannabis cigarettes is known to suppress both hormonal and cell-mediated immune responses. There appears to be no evidence of teratogenicity resulting from cannabis exposure. However, low neonatal birth weight, increased risk of complications during labor, and delay in cognitive development in infants, have been reported in cannabis addicted-parturients. Additional studies on this subject are needed.

Anesthetic Implications

The cardiovascular effects of marijuana (myocardial depression and tachycardia) may potentiate the effects of anesthetic drugs affecting HR and BP. Adverse interactions of marijuana with propranolol and phystostigmine have been reported. Cannabis may enhance the sedative-hypnotic effects of other drugs that depress the CNS. Studies have shown cross-tolerance of cannabis with alcohol, barbiturates, opioids, benzodiazepines, and phenothiazines. During general anesthesia, additive effects of marijuana and potent inhaled anesthetics can result in pronounced myocardial depression. In parturients with a history of acute marijuana abuse, drugs that increase HR such as ketamine, pancuronium, atropine, and epinephrine should be avoided. Cannabis inhalation leads to impairment of lung function similar to tobacco smoking. Oropharyngitis and uvular edema causing airway obstruction during general anesthesia have been reported. Additionally, adverse psychiatric and autonomic reactions to cannabis may interfere with safe induction of anesthesia and postoperative recovery.

Ethanol

Epidemiology and Pathophysiology

Ethanol is the substance that is commonly abused in pregnancy, and many maternal and fetal complications resulting from ethanol addiction have been identified. Alcoholism is the third leading cause of death and disability in the United States. More than 15 million people in the United States are addicted to alcohol, with women accounting for approximately 25% of this number. Evidence suggests that alcohol consumption in pregnancy causes adverse fetal sequelae at any stage of fetal development and any gestational age. Unfortunately, the possibility of alcoholism is often overlooked in pregnant patients, because the effects of alcohol addiction are often more subtle and more difficult to diagnose.

Diagnosis and Clinical Presentation

The intoxicating effects of alcohol parallel its plasma concentration. A blood alcohol level of 25 mg/dL is associated with impairment of cognition and coordination. Intoxication is usually defined as a blood alcohol level greater than 100 mg/dL. When ethanol is compared with other commonly abused substances, the effects of alcohol addiction are often more subtle and more difficult to diagnose. Chronic alcohol consumption may result in malnutrition, liver disease, altered drug metabolism, coagulopathy, pancreatitis, esophageal varices, and cardiomyopathy. Acute alcohol intoxication increases gastric fluid acidity and volume, with simultaneous decrease in the ability to protect the airway. If heavy alcohol ingestion is not associated with food intake, pronounced hypoglycemia may occur.

Interaction with Pregnancy

Ethanol easily crosses the placental barrier and has well-established teratogenic properties. Ethanol consumption in pregnancy may lead to the Fetal Alcohol Syndrome (FAS), which was first described in France in 1968. The incidence of FAS varies with inclusion criteria and geographical location. The syndrome involves a spectrum of symptoms including IUGR, characteristic facial appearances, mental handicap, and musculoskeletal, genitourinary, and cardiovascular abnormalities. Neurotoxicity of ethanol exposure of the fetus, including myelination abnormalities and optic nerve hypoplasia, have been reported. Neurologic effects of ethanol appear to be mediated by its actions on the inhibitory neurotransmitter, gamma aminobutyric acid (GABA).

The overall neonatal mortality in pregnancies complicated by heavy alcohol intake is estimated at 18%. To date, no safe level of alcohol consumption in pregnancy has been established. Regardless of the gestational period, alcohol causes adverse fetal effects; therefore, abstinence from alcohol appears the safest approach in pregnancy.

Anesthetic Implications

Ethanol-abusing parturients, depending on degree of chemical dependency and timing of the most recent drug intake, may present to labor and delivery with a variety of clinical manifestations. Physiologic dependence on alcohol is manifested as a withdrawal syndrome when the drug is abruptly discontinued or when there is a significant decrease in the intake. The most common and earliest manifestations of acute withdrawal include generalized tremor, hypertension, tachycardia, cardiac arrhythmias, nausea, vomiting, insomnia, and confusion with agitation and hallucinations. Symptoms of acute withdrawal usually begin 6 to 48 hours following cessation of alcohol consumption, although delay as long as 10 days after last intake has been reported. The withdrawal symptoms may be suppressed by the administration of benzodiazepines, α2 adrenergic agonists, or resumption of alcohol consumption. Delirium tremens is a rare, although life-threatening medical emergency in ethanol-addicted parturients. Acute alcohol intoxication may pose a significant risk of pulmonary aspiration to the mother and “fetal distress” to the fetus.

Regional anesthesia can be safely administered to parturients with a history of alcohol abuse. Contraindications include infection and coagulopathy, which are usually
encountered in end-stage disease.2,51 Neuropathy also should be considered as a medicolegal contraindication to regional anesthesia. Intravascular fluid volume must be optimized before induction of regional anesthesia to avoid adverse consequences of sympathetic blockade. Preexisting neurologic impairment should be documented to avoid future litigation.

If general anesthesia is deemed necessary, associated hepatic dysfunction, hypoalbininemia, and cardiac failure may require appropriate dose adjustments of IV induction drugs. Chronic use of alcohol is usually associated with resistance to the actions of CNS depressants. However, suggestions that chronic ethanol consumption necessitates increased requirements of barbiturates have not been confirmed.125 Similarly, the use of excessive concentrations of potent inhaled anesthetics can lead to cardiovascular depression. On the contrary, acutely intoxicated parturients require less anesthetic. The risk of aspiration is increased in these parturients due to increased gastric fluid volume and acidity, as well as impaired laryngeal reflexes.

Tobacco

Epidemiology and Pathophysiology

Approximately 80% of women who smoke before pregnancy continue to smoke when pregnant.126 Low cigarette consumption before pregnancy is the best predictor for smoking cessation in pregnancy. In a national survey conducted in Norway, 21% of pregnant women reported smoking daily in the second trimester of pregnancy.127 In 1990, it was reported that more than 29% of women of childbearing age in the United States smoked cigarettes.128 Others have estimated that approximately 30% of all women smoke during pregnancy.22

Diagnosis and Clinical Presentation

Cigarette smoking affects pulmonary function primarily. The irritant effect of smoke decreases ciliary motility, increases sputum production, and impairs gas exchange. Tobacco smoke is composed of more than 1,000 components, of which nicotine, carbon monoxide, and hydrogen cyanide are the most harmful. Nicotine can decrease placental blood flow due to vasoconstriction and contribute to development of fetal hypoxia.129 The affinity of hemoglobin for carbon monoxide is 200 times its affinity for oxygen, which results in decreased oxygen delivery to maternal and fetal tissue.130 Normally in nonsmoking individuals, the carboxyhemoglobin concentration is less than 1%. However, in smokers, it increases significantly and can be as high as 7% to 10%. Smoking is associated with an increase in the rate of development of atherosclerosis. Smokers have a dramatically increased prevalence of peripheral vascular disease, coronary artery disease, and a 3.5-fold increased risk of acute MI.

Interaction with Pregnancy

The effects of smoking on the fetus may be a result of any of the 1,000 chemical substances detected in tobacco smoke. Unfortunately, apart from nicotine and carbon monoxide, very little is known about the effects of other toxins in tobacco smoke on the fetus. It has been reported that tobacco-specific carcinogens found in tobacco smoke easily cross the placenta and can significantly affect the fetal development. Metabolites of potent tobacco-specific carcinogen 4-(methylnitrosamo)-1-(3-pyridyl)-1-butanone (NNK) have been detected in the urine in 71% of newborns of parturients who smoked during pregnancy.131 The chemical composition of tobacco smoke seems more closely related to fetal IUGR than the actual number of cigarettes smoked. Tobacco abuse in pregnancy has been associated with spontaneous abortion, IUGR, premature rupture of membranes, and preterm labor. Heavy tobacco abuse has resulted in placental abruption and sudden infant death syndrome (SIDS).132,133 In fact, smoking has been proven to be one of the most important preventable risk factors for SIDS.134

Anatomical changes in the human placenta, such as thickening of the trophoblastic basal membrane, focal necrosis, and hypertrophy, have been reported in parturients who smoke.135 Functional physiologic alterations such as vascular constriction, decreased placental perfusion, and impaired oxygen exchange may occur and adversely affect fetal development and pregnancy outcome. The number of low-birth-weight (LBW) infants increases in proportion to the number of cigarettes smoked.136 Intrauterine fetal growth seems to be negatively affected not only by active smoking, but also by passive exposure to cigarette smoke.137 Older parturients who smoke cigarettes during pregnancy appear to be at higher risk than younger women of delivering small-for-gestational-age (SGA) or LBW infants.138 Interestingly, the incidence of PIH may be decreased in women who smoke during pregnancy.139

Many women continue to abuse tobacco during pregnancy, despite the well-documented hazardous health effects of smoking.140 The rate of tobacco abuse in pregnancy for women between 15 and 19 years of age decreased between 1990 and 1994, but it increased afterwards. Today, this age group has the highest smoking rates of all age groups. ACOG places strong emphasis on cessation of tobacco abuse in pregnancy. Educational and behavioral approaches, as well as nicotine replacement therapy, have been recommended for tobacco-abusing parturients.141 A transdermal nicotine patch allows pregnant women to receive nicotine without exposure to the other chemicals found in cigarette smoke. Parturients, who for various reasons are not suitable candidates for nicotine replacement therapy, may receive bupropion (an antidepressant with adrenergic and dopaminergic actions) in sustained-release tablets.142 The drug works equally well in the presence and absence of depression, suggesting that its mechanism of action is not due to antidepressant properties.143,144
Anesthetic Implications

Cigarette smoke primarily affects respiratory system function. Pulmonary effects of tobacco abuse include an increase in secretions and sputum production, decrease in ciliary motility, small airway dysfunction, and impairment of gas exchange.142 In smokers, 4 to 6 weeks of abstinence from tobacco smoke is required to decrease postoperative respiratory morbidity to the level of a non-smoker. However, any period of abstinence is recommended, and as little as a few days can improve mucociliary function. In tobacco-abusing patients who undergo as little as 48 hours of abstinence, levels of carboxyhemoglobin may return toward those levels seen in nonsmokers. Cigarette smoke may affect hepatic enzyme function and alter the metabolism of induction drugs used for general anesthesia. Therefore, neuraxial anesthetic techniques seem particularly suitable for tobacco-abusing parturients. Intraoperative complications resulting from tobacco abuse, such as bronchospasm, as well as postoperative respiratory dysfunction, can be avoided with the administration of regional anesthesia and avoidance of airway manipulation.

Caffeine

Epidemiology and Pathophysiology

Caffeine is a methylxanthine found in a variety of products such as tea, coffee, cola, and cocoa. Most Americans consume caffeine daily in one of its many forms. A cup of coffee, depending on its strength, contains 29 to 176 mg of caffeine. It has been reported that approximately 80% of women drink caffeine-containing beverages daily.

Diagnosis and Clinical Presentation

Clinical research indicates that withdrawal symptoms can occur when daily consumption of caffeine is abruptly interrupted.107,146 The caffeine physical dependence syndrome may lead to postoperative complications such as headache, nausea, vomiting, and musculoskeletal aches. Most commonly, however, abrupt discontinuation of regular daily caffeine intake will lead to anxiety, mild to moderate headache, and muscle aches.107,147

Interaction with Pregnancy

Caffeine is readily absorbed from the mucosa of the gastrointestinal tract. It crosses the human placenta, rapidly reaching concentration in the fetus similar to maternal plasma levels.148,149 Historically, caffeine has been implicated as a cause of spontaneous abortion, IUGR, LBW, and preterm delivery. However, a recent study found no evidence that moderate caffeine use in pregnancy may affect hepatic enzyme function and alter the metabolism of induction drugs used for general anesthesia. Therefore, neuraxial anesthetic techniques seem particularly suitable for tobacco-abusing parturients. Intraoperative complications resulting from tobacco abuse, such as bronchospasm, as well as postoperative respiratory dysfunction, can be avoided with the administration of regional anesthesia and avoidance of airway manipulation.

Anesthetic Implications

Symptoms of caffeine withdrawal may occur during labor or in the parturient fasting before or after abdominal delivery. A significant relationship exists between daily caffeine intake before surgery and the incidence of postoperative headache.146,155 If regional anesthetic techniques are selected, differentiation between postdural puncture headache (PDPH) and caffeine withdrawal headache should be considered in parturients reporting postpartum headache.

Summary

Despite ongoing preventive and rehabilitative efforts at the local, national, and international level, substance abuse by parturients continues to increase worldwide. The diagnosis of drug abuse in pregnancy is no longer uncommon. The diverse clinical manifestations of substance abuse combined with physiologic changes of pregnancy, and pathophysiologic of coexisting pregnancy-related disease may lead to life-threatening complications and significantly impact the practice of obstetric anesthesia. Careful preanesthetic evaluation combined with judgment-free questioning of possible illicit substance intake is essential, if not of primary importance. Anesthetic management should be tailored to individual patient needs and the urgency of obstetrical indications for either vaginal or abdominal delivery.

The challenges of the anesthetic management of obstetric patients with a history of drug abuse, either electively or urgently, are many. A complete understanding of the physiology of pregnancy, pathophysiologic of pregnancy-specific disorders, and anesthetic implications of drug abuse in pregnancy is essential to tailor a safe anesthetic plan for these high-risk groups of patients.

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