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Pregnancy and Cardiovascular Disease (N Scott, Section Editor)

Management of the Cardiovascular Complications of Substance Use Disorders During Pregnancy

P. Kaitlyn Edelson, MD[*]
Sarah N. Bernstein, MD

Address
[*]Department of Obstetrics and Gynecology Founders 4, Massachusetts General Hospital, 55 Fruit Street, Boston, MA, 02114, USA
Email: pkedelson@mgh.harvard.edu

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Abstract

Purpose of review Substance use disorder in pregnancy and subsequent cardiovascular complications are on the rise in the USA. The care of pregnant women with substance use disorder is complex, and requires a thorough understanding of mechanisms of action, pathophysiology, and cardiovascular response during pregnancy. The goal of this review is to provide information about the most common drugs of abuse in pregnancy and to recommend management guidelines.

Recent findings Pregnant women with substance use disorder are at increased risk of significant cardiovascular complications, both as a direct effect of acute intoxication as well as the secondary risk from infection and cardiotoxicity associated with chronic use. This risk must be considered in the antepartum management, delivery, and postpartum periods.

Summary Understanding the increased cardiovascular risk of pregnant women with substance use disorder, as well as specific drug interactions, anesthesia considerations, best practices, and management considerations, is important for all clinicians caring for this population.

Introduction

Illicit substance use during pregnancy can cause significant and complex changes to maternal cardiovascular function. Such changes contribute to adverse maternal and fetal outcomes during pregnancy, at the time of delivery, and in the postpartum period. Provider knowledge of the mechanisms of action, effects, and interactions of these substances in the setting of pregnancy is essential to optimize care for women with substance use disorders. The specific focus of this review is to describe pathophysiologic cardiac effects of commonly used substances in pregnancy and to discuss management considerations in the antenatal, intrapartum, and postpartum context. We will review the drugs with the most significant cardiovascular implications: cocaine, opioids, alcohol, and amphetamines.

Substance use disorder (SUD) is defined by the *Diagnostic and Statistical Manual of Mental Disorders-5* as a pattern of symptoms resulting from the continued, harmful use of substances despite adverse effects. The formal diagnosis requires the presence of specific physical and psychological symptoms. Severity is correlated with the number of criteria met. (1) The term substance use disorder encompasses both substance use and dependence, and includes 10 separate drug classes (alcohol, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants, and tobacco) [1]. These substances can be more broadly classified into hallucinogens, stimulants, and depressants [2].

SUD is on the rise in the USA, including amongst pregnant women. For opioid use disorder alone, the prevalence in pregnant women quadrupled from 1.5 per 1000 delivery hospitalizations to 6.5 per 1000 between 1999 and 2014 [3]; opioid use amongst pregnant women has increased by 333% from 2004 to 2017 [4]. In a 2012 national survey of pregnant women, 8.5% consumed alcohol and 5.9% used illicit drugs [5]. SUD in pregnancy is associated with significant maternal and fetal morbidity and mortality. Polysubstance use is highly associated with mental health conditions. In one study, 65% of opioid using women endorsed mental health symptoms. Specifically, 40% endorsed anxiety, 32% endorsed depression, and 12.6% endorsed suicidal thoughts in the last 30 days [6]. Overdose is a major unrecognized cause of maternal mortality and one of the top causes in several states in the USA [7]. Additionally, SUD in pregnancy is more common in poorer, less educated women, and puts them at risk for worse obstetric and birth outcomes, including infectious disease, prematurity and low birthweight, placental abruption, and fetal death [8, 9]. Pregnant women with SUD are also more likely to have poor nutrition, have multiple chronic medical conditions, receive inadequate prenatal care, and higher rates of hospitalization and emergency room use during pregnancy [8].

Cardiovascular changes in pregnancy

Multiple physiologic cardiac changes occur in pregnancy, including increased cardiac output, increased heart rate, increased plasma volume, reduced systemic vascular resistance, and relative anemia from hemodilution [10]. These normal physiologic changes, which are well-tolerated in the majority of pregnant women, can be rapidly accelerated or blunted in the setting of active substance use, leading to potentially catastrophic cardiac effects [11]. Specific considerations for each drug are discussed in detail below (Table 1).

Cocaine

Mechanism

Cocaine is an adrenergic stimulator and blocks the presynaptic uptake of sympathomimetic neurotransmitters (norepinephrine, serotonin, and dopamine), thus prolonging their effect and inducing euphoria [15, 16]. Cocaine is

Table 1. Commonly used substances of abuse and their effects in pregnancy

	Cocaine	Opioids	Alcohol	Amphetamine
Mechanism	-Inhibits reuptake of catecholamines -Sodium channel blockade	-Increase parasympathetic tone -Decrease sympathetic tone -Histamine release from mast cells	-Increase gamma aminobutyric acid (GABA)	-Release catecholamines from nerve terminals
Cardiac effects	-Hypertension -Arrhythmia -Vasoconstriction	-Hypotension -Arrhythmia -Infectious complications if used intravenously	-Direct cardiomyocyte toxicity -Arrhythmia -Dilated cardiomyopathy with chronic use	-Hypertension -Arrhythmia -Acute heart failure
Pregnancy considerations	-Preterm birth / premature rupture of membranes -Placental abruption -Spontaneous abortion	-Preterm birth / premature rupture of membranes -Small for gestational age -Neonatal abstinence syndrome	-Preterm birth / premature rupture of membranes -Small for gestational age -Spontaneous abortion -Fetal alcohol spectrum disorder	-Preterm birth / premature rupture of membranes -Placental abruption -Spontaneous abortion -Neonatal withdrawal symptoms

Compiled from references: [2, 12–14]

ingested by smoking, intra-nasally, and by intravenous injection. The half-life is 0.5–1.5 h, and it is metabolized by the plasma and liver cholinesterases prior to being excreted in the urine [17]. It can be detected in the urine 3–6-h post-use, and metabolites can be detected up to 60-h post-use [18]. While the most acute cardiovascular period appears to be in the first hours following ingestion, it is important to note that severe cardiovascular events can occur even > 24-h post-use [15].

The cardiovascular effects of cocaine occur predominantly due to increased levels of plasma catecholamines [19]. Life-threatening cardiovascular complications following acute cocaine intake can include hypertension, tachycardia,

malignant arrhythmias, myocardial ischemia and infarct [20], and less commonly aortic dissection and stroke [21]. Mechanisms of cocaine-induced myocardial ischemia likely include a combination of thrombosis, vasospasm of the coronary arteries, and direct myocardial depression [22]. With chronic use, this can result in a cocaine-associated dilated cardiomyopathy [23]. Cocaine-induced thrombocytopenia and associated microangiopathy have been described in both pregnant and non-pregnant individuals [24].

Pregnancy considerations

Pregnancy appears to enhance the direct cardiovascular toxicity of cocaine due to progesterone causing increased metabolism of cocaine to norcocaine [15]. Cocaine increases the risk of pre-eclampsia, placental abruption, preterm labor by placental vasoconstriction, and increased uterine irritability [25, 26] Cocaine crosses the placenta [27], and prenatal exposure increases the risk of intra-uterine growth restriction, limb reduction defects, in-utero infarction or hemorrhage, and intra-uterine fetal demise [28]. The mechanism of these vascular events is direct vasoconstriction and spasm of the uterine arterial supply [25].

Catastrophic cardiac events including myocardial infarction have been reported in the peripartum period with even small quantities of cocaine ingestion [29]. Cesarean section should be reserved for the usual obstetric indications. Similar to routine obstetrical care, regional anesthesia is preferred when feasible; however, close attention to hemodynamics is necessary due to vasoconstriction, hypertension, and potential arrhythmia [12, 15]. Management of hypertension in the setting of acute cocaine intoxication is challenging, and beta-blockers are contraindicated due to unopposed alpha-adrenergic stimulation, resulting in coronary artery vasospasm and paradoxical hypertension [15].

Opioids

Mechanism

An opioid is a psychoactive chemical that binds to opioid receptors, primarily mu, kappa, and delta, located in the central nervous system and gastrointestinal tract [30]. The primary effect of opioids is decreased perception of pain, increased pain tolerance, and euphoria. Opioid dependence is common and withdrawal occurs within 6–12 h of heroin use, though long-acting opioid use extends the withdrawal period to 72–96 h [31]. The primary routes of administration are oral, intravenous, intra-nasal, and smoking [32]. Whereas long-acting opioid formulations exert an effect for 12–16 h, the duration of heroin euphoria lasts 3–5 h, though the rate of opioid metabolism can vary significantly between individuals during pregnancy [33].

Pregnancy considerations

The prevalence of opioid use disorder in pregnancy has increased dramatically in the last two decades. In an analysis of the National Inpatient Sample from 1998 to 2011, which included over 56.9 million deliveries, the risk of cardiac arrest in a pregnant woman with opioid use disorder was 3.6-fold that of a non-opioid use disorder woman [9]. Opioids cross the placenta and have been found in amniotic fluid within 1 h of ingestion with minimal metabolism [34]. Studies

evaluating the teratogenicity of opioids show mixed results, with small increases in oral cleft, ventricular septal defects, and club foot noted in small studies [35]. Opioid use in pregnancy is associated with intrauterine growth restriction, preterm labor, maternal infection, and neonates at risk for neonatal abstinence syndrome (NAS) [32]. NAS is a transient and treatable condition that is sometime seen in babies of mothers taking both prescribed opioid maintenance therapy as well as illicit opioids. The severity of NAS and duration of inpatient neonatal treatment is difficult to predict antenatally, but it is thought to affect between 45 and 94% of fetuses exposed to opioids in utero [36].

For opioid use disorder, treatment with an opioid agonist is considered standard of care in pregnancy [13, 37]. It has been shown to decrease the rates of relapse and improve obstetric outcomes including decreasing preterm birth rates [38] and rates of fetal growth restriction [39]. Methadone and buprenorphine are the two most common medications used in pregnancy, and both are considered safe and effective. Methadone has been shown to cause hypoventilation and blunt the maternal heart rate response to exercise, thus blunting the normal compensatory hyperventilation that occurs in pregnancy [40]. Methadone can prolong the QT interval, and this effect has been found to be more pronounced in the pregnant population and appears to be correlated with dose [41, 42]. Given this anticipated prolongation of QT complex, it is essential that patients have an EKG with each dose increase, and additional QT prolonging medications should be avoided when possible.

Illicit opioid use confers multiple cardiovascular risks in pregnancy, including arrhythmia and cardiac arrest. Though the mechanism of cardiac dysfunction is not clear, it is hypothesized that opioid use during pregnancy compromises coronary circulation and normal conduction of the heart, potentially leading to myocardial infarction and cardiac arrest [43]. A specific concern with intravenous administration of heroin is the potential for infectious disease transmission, both maternal infection with HIV, hepatitis, and other blood-borne pathogens, as well as ascending injection site infection, which has been associated with maternal peripartum infective endocarditis and sepsis [44].

In women with a history of intravenous opioid use, infective endocarditis must be considered. The most commonly affected valve is the tricuspid valve, likely due to ascending intravenous infection, though other valves can also be affected [45]. Infective endocarditis of the tricuspid valve can then progress to tricuspid regurgitation. This valvular pathology is typically well-tolerated in pregnancy even in the setting of increased plasma volume during the third trimester. However, a recent meta-analysis of infective endocarditis in the peripartum period found a maternal mortality rate of 11% and an intra-uterine fetal demise rate of 20% [45].

Infective endocarditis requiring urgent valve replacement is rare in pregnancy. There have been case reports of peripartum cardiac tamponade secondary to aortic dissection in the setting of infective endocarditis from intravenous drug use, requiring simultaneous delivery and valve repair [46]. The management of prosthetic valves in pregnancy requires an interdisciplinary team of cardiologists and maternal-fetal

medicine physicians, and the decision for mode of delivery and duration of anticoagulation is complex.

Alcohol

Mechanism

Alcohol affects the brain by increasing gamma-aminobutyric acid (GABA), which is an inhibitory neurotransmitter [47].Alcohol is known to be directly toxic to cardiomyocytes, and dilated cardiomyopathy can result with chronic use [48].

Pregnancy considerations

Alcohol use in pregnancy is widespread, with 12.5% of the pregnant population in the USA reporting some alcohol use in pregnancy [49], and 3.6% of pregnant women meet criteria for alcohol use disorder [50]. Alcohol withdrawal in pregnancy is associated with physiologic instability, hypertension, tachycardia, seizure, hyperthermia, hallucination and death, and must be managed vigilantly [51]. Due to societal pressures and newfound motivation in the setting of pregnancy, it is not uncommon for women to present in acute withdrawal, which can result in severe maternal electrolyte and hemodynamic instability, arrhythmia, seizures, or delirium tremens [52]. In pregnancy, alcohol has been shown to decrease uteroplacental perfusion, resulting in intra-uterine growth restriction [53]. Additionally, if alcohol use is chronic, hepatic dysfunction may be present and screening should occur early in pregnancy. The effects of alcohol on the developing fetus are highly variable and depend on the timing of exposure, chronicity of exposure, and dose of exposure [53]. Fetal alcohol syndrome disorder (FASD) is a constellation of symptoms including facial dysmorphology, growth deficiency, central nervous system dysfunction, and neurobehavioral impairment associated with exposure to alcohol during pregnancy [54].

Amphetamines

Mechanism

Amphetamines are synthetic, non-catecholamine sympathomimetic drugs that directly stimulate the central nervous system. They cause the release of norepinephrine, dopamine, and serotonin from nerve endings, and increase the concentrations of these neurotransmitters, which increase nerve transmission. The effects of amphetamines are euphoria, wakefulness, and social inhibition. The half-life is approximately 12 h [28]. The route of ingestion is smoking, intravenous injection, or oral. The cardiac effects of amphetamines are tachycardia, hypertension, and arrhythmia [32].

Pregnancy considerations

In pregnancy, amphetamines stimulate a large norepinephrine response, which in turn causes tachycardia, hypertension, and increased cardiac output. Amphetamine use has also been associated with pre-eclampsia and abruption. Amphetamines cross the placenta and cause direct vasoconstriction [14]. Amphetamine exposure in utero is associated with preterm birth, low birthweight, spontaneous abortion, and childhood behavioral deficits.

Pregnancy, delivery, and postpartum considerations

Fetal risk assessment

Pregnant women with SUD are at increased risk of congenital malformations related to specific substances used and should be offered a complete fetal anatomic survey between 18 and 22 weeks gestation in conjunction with a maternal-fetal medicine consult. If specific concerns arise on ultrasound, a fetal echocardiogram or MRI may be indicated. Exposed fetuses should also be screened for growth restriction in the third trimester. If substance use is ongoing throughout the pregnancy, additional antenatal fetal surveillance may be warranted.

Antenatal and delivery management

General approach to prenatal care and substance use disorder

Universal screening for SUD should take place pre-conception, during the initial OB intake visit, and ideally in the third trimester or on presentation for delivery. There are many validated screening tools available; none of which have been found superior in the setting of pregnancy [55]. The following patient characteristics have been described as risk factors for SUD: age < 25 years, household income level at or below poverty level, high school education or less, concurrent psychiatric disorder, trauma history, and family history of substance use disorder [2].

Once a SUD is identified, a multidisciplinary team should ideally be assembled, including obstetricians with either primary management or consultation with maternal-fetal medicine physicians, addiction medicine, psychiatry, social work, and anesthesia and neonatology consults as delivery approaches (Fig. 1). A detailed history of prior substance use should be undertaken to include specific details of duration and type of substances used, last use, and associated hospitalizations and medical complications. Special attention should be paid to intravenous access in patients with a history of intravenous drug use; if there is known difficulty with intravenous access, this should be well documented in the patient's chart, and early access should be obtained. In the setting of opioid use disorder, offering the patient a prescription for home naloxone is a reasonable harm-reduction strategy to prevent overdose should relapse occur. If there is a history of cardiac complications, a cardiology referral may be appropriate.

The detection of underlying cardiovascular pathology in pregnant women with substance use disorder can be difficult given the normal physiologic changes of pregnancy which can create shortness of breath, mild tachycardia, and gastro-esophageal reflux, which can mimic the symptoms of cardiac disease. A high level of suspicion is appropriate when considering a patient's risk factors, substance use history, and physical exam. If underlying cardiovascular disease is suspected, baseline maternal echocardiogram and electrocardiogram are indicated. If cardiovascular disease is diagnosed, close co-management with a cardiologist and maternal fetal medicine specialist is warranted. An anesthesia consultation in the third trimester may be helpful for labor and delivery planning. Volume status should be carefully monitored. Echocardiograms can be obtained at baseline as needed for worsening symptoms and at 32 weeks as this is the time that pregnancy-related blood volume is at its peak.

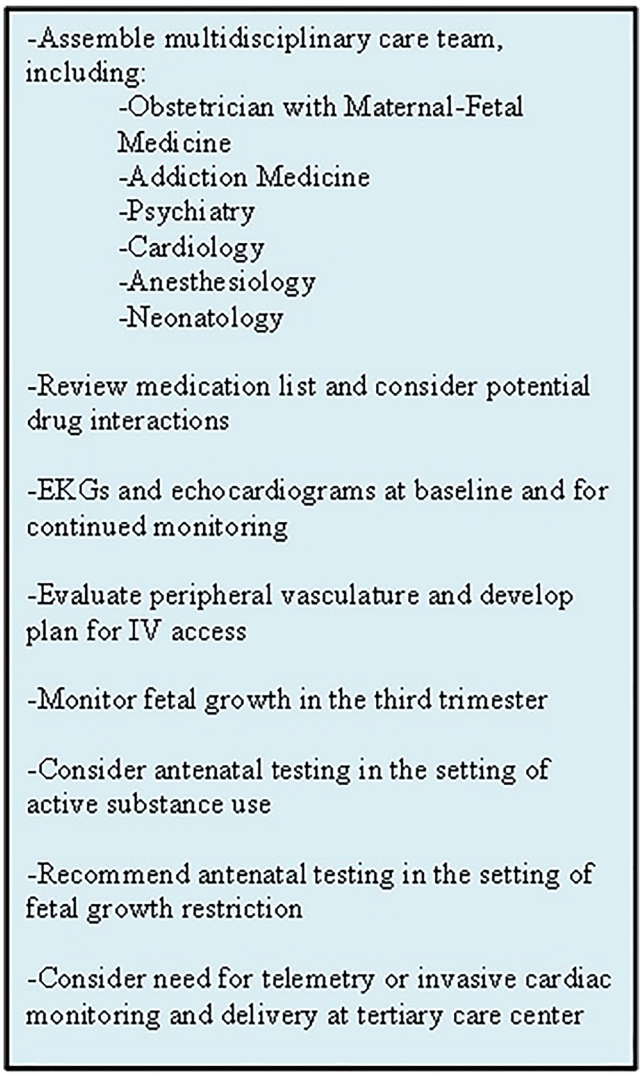

Fig. 1. Approach to the patient with SUD in pregnancy and cardiovascular disease.

Obstetric emergencies

Acute intoxication

If acute intoxication is suspected in the setting of pregnancy, maternal and fetal wellbeing must be rapidly evaluated, ideally with the assistance of an obstetrician and/or maternal-fetal medicine physician and anesthesiologist. Once maternal vital signs are assessed, both fetal viability and estimated gestational age should be determined either by ultrasound or fundal height. If possible, a history of the type and use of substances should be obtained.

If the fetus is greater than 24-week gestation, various tools can be utilized to assess fetal well-being, including ultrasound and electronic fetal monitoring. If

Table 2. Commonly used medications in pregnancy interactions with substances of abuse

	Cocaine	Opioids	Alcohol	Amphetamine
Beta-blockers	-Risk of unopposed alpha adrenergic stimulation and hemodynamic instability			
Calcium channel blockers			-Risk of hypotension and potentiation of calcium channel blockade	
Terbutaline	-Risk of hypertension, tachycardia and myocardial infarction	-Risk of prolonged QT		-Risk of hypertension and tachycardia
Ondansetron		-Risk of prolonged QT		
Methergine	-Risk of hypertension	-Risk of increased serotonin response and serotonin syndrome		-Risk of hypertension -Risk of increased serotonin response and serotonin syndrome
Hemabate				
Magnesium		-Risk of central nervous system depression	-Risk of central nervous system depression	

Data from references: [2, 12, 14]

contractions are detected on external tocometer, then an assessment for preterm labor or abruption may be indicated. Interpretation of fetal monitoring in the setting of recent substance use can be challenging as ingested substances can cause transient concerning patterns that are difficult to distinguish from patterns due to chronic uteroplacental insufficiency.

Obtaining urine toxicology studies is essential, but there may be a significant delay in obtaining the results, making the physical exam of utmost importance, including a basic eye exam to assess for dilation or constriction of pupils. A baseline EKG and serum labs should be obtained as electrolyte disturbances are common and need to be corrected. The anesthesia team

should be urgently notified to help assess the patient's airway and intravenous access as well as plans for delivery if needed. If it is not clear what drug was recently used, it is important to avoid potential exacerbating medications prior to the urine toxicology results. If opioids or alcohol were recently used, the QT interval should be assessed and if there is a prolonged QT, then prolonging medications should avoided (Table 2). If cocaine intoxication is suspected, extreme caution should be used with beta-blocker administration due to the concern for unopposed alpha stimulation, which can result in coronary vasoconstriction and spasm [56]. Additionally, terbutaline, a beta-2 agonist commonly used to promote uterine relaxation in the setting of fetal distress in labor, should be avoided to decrease the risk of maternal arrhythmia and hemodynamic instability.

Placental abruption

Placental abruption occurs when the placenta separates prematurely from the uterus, often in the setting of hypertension and/or vasoconstriction as is seen in acute intoxication with cocaine, amphetamines, or opioids. This separation can result in rapid and severe maternal disseminated intravascular coagulation, hemorrhage, and exsanguination, as well as fetal distress and intrauterine fetal demise. The rate of abruption is 3.1-fold higher in women with SUD as compared to women without SUD [57]. Clinically, vaginal bleeding or regular contractions in the setting of recent substance use is highly concerning for abruption, and rapid assessment should include maternal hemodynamic status, serum labs including type and crossmatch, complete blood count, clotting times and fibrinogen, and rapid establishment of reliable intravenous access. Anesthesia should be alerted, and preparation for possible transfusion should be undertaken. The obstetric management of acute severe abruption is urgent delivery; mode of delivery depends on maternal and fetal status.

Postpartum care

Immediately following delivery, maternal cardiac output increases by 50% and stroke volume increases by 60%, due to autotransfusion from the postpartum uterus [58]. Within the first 24 h of delivery, there are large volume shifts that occur with a sudden increase in intravascular volume; these changes are even more pronounced after a cesarean section. In a patient with underlying cardiac disease, specifically valvular disease or cardiomyopathy, close attention must be paid to volume status, intravenous fluid administration, and urine output. Diuresis may be necessary if a patient becomes fluid overloaded. Monitoring of electrolytes is also crucial during this time period, particularly in patients who may have recently used drugs that provoke arrhythmia, and telemetry monitoring may be indicated.

Contraception

Per ACOG guidelines for care of pregnant women with SUD, all women should be offered contraception [59]. The United States Medical Eligibility Criteria guidelines for contraception do not exclude women with SUD or many cardiovascular conditions from receiving any specific type of contraceptive, and so a woman with SUD should be counseled regarding her full range of options, including highly effective LARC methods [60].

Summary and conclusions

Given the rise of SUD in pregnancy, providers should be familiar with common cardiovascular complications and medication interactions that occur in the antenatal, intrapartum, and postpartum periods.

Successful management of SUD in pregnancy requires a multidisciplinary team approach.

The patient should be counseled about the importance of family planning utilizing long action options like IUDs and progesterone implants with a goal of stabilization prior to conceiving.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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