Fetal Surveillance in Late Pregnancy and During Labor

Luis A. Izquierdo, MD, MBA[a,*], Nicole Yonke, MD, MPH[b]

KEYWORDS

• Illegal substance abuse • Mother • Fetus • Antepartum testing

KEY POINTS

- During early gestation, drugs have teratogenic effects and can be associated with structural anomalies in the fetus.
- Substance abuse can have physiologic effects on the mother and fetus, including decreased uterine blood flow, increased vascular resistance, and an increase in fetal blood pressure.
- Women with increased risk for stillbirth should undergo antepartum fetal surveillance using a nonstress test (NST), contraction stress test, biophysical profile (BPP), or modified BPP.
- Initiating antepartum fetal testing at 32 weeks of gestation is appropriate for most pregnancies at an increased risk of stillbirth.
- Because of the high incidence of low birth weight, fetal anomalies, preterm delivery, and growth restriction, obtaining an ultrasonogram for appropriate pregnancy dating, a detailed anatomic survey, and cervical length at 20 weeks of gestation is recommended.
- In patients who are abusing stimulants such as methamphetamines and cocaine, fetal growth should be closely followed every 3 to 4 weeks and, owing to the generalized vasoconstriction that these patients develop, antenatal testing should be started routinely at 32 weeks with twice-weekly NSTs and a once-weekly modified BPP.

INTRODUCTION

Once gestation is beyond 20 weeks, clinicians have to address the impact of illicit substances on fetal growth, placentation, and the possibility of early delivery. Cannabis remains the most commonly used illicit drug in the United States.[1] Other agents used by pregnant patients include heroin, cocaine, hallucinogens, inhalants, alcohol,

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[a] Division of Maternal Fetal Medicine, University of New Mexico School of Medicine, MSC 105580, 1 University of New Mexico, Albuquerque, NM 87131, USA; [b] Division of Maternal Child Health, University of New Mexico School of Medicine, 1 University of New Mexico, Albuquerque, NM 87131, USA
* Corresponding author.
E-mail address: lizquierdo@salud.unm.edu

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and prescription psychotherapeutics.[2] An estimated 4.4% of pregnant women report illicit drug use in the preceding 30 days.[3] During early gestation drugs have teratogenic effects, and can be associated with structural anomalies in the fetus.[4,5] Substance abuse can have physiologic effects on the mother and fetus, including decreased uterine blood flow, increased vascular resistance, and an increase in fetal blood pressure.[1] As pregnancy advances, these substances can have more subtle effects that can lead to abnormal fetal growth, alterations in fetal growth, alterations in neurotransmitters and their receptors, and brain organization.

The effects of illegal substance abuse during pregnancy should be addressed with caution given the nature of the available evidence. Investigators have raised at least 4 issues that are of particular concern when analyzing these data:

1. The difficulty of accurately measuring illicit substance-use patterns in women throughout pregnancy.
2. The difficulty in separating the effects of drug use from the effects of other adverse confounding personal and social circumstances.
3. The existence of a common pattern of polysubstance use in this population.
4. Possible publication bias or apparent reviewer editorial bias that results in preferential publication in the scientific literature of studies that show unfavorable outcomes in association with substance use.[6]

This article describes the effects of substance use during pregnancy on fetal growth and surveillance in the antepartum and intrapartum period, based on the research available and the authors' own clinical experience.

MATERNAL AND FETAL CONSEQUENCES OF ILLICIT SUBSTANCE USE IN PREGNANCY

Marijuana or Cannabis

As already mentioned, marijuana is one of the most commonly used drugs in the United States during pregnancy, and its use appears to be increasing steadily in those aged 12 years or older.[3] Δ9-Tetrahydrocannabinol is the active ingredient in marijuana, and readily crosses the placenta. Of importance is that marijuana produces higher blood carboxyhemoglobin levels than are produced by cigarette smoking. These higher concentrations of carboxyhemoglobin can affect fetal oxygenation and, ultimately, fetal growth and development.[3]

Opioids

Addiction to opioids can develop by repetitive use of either prescription opioid analgesics or heroin.[4] Heroin is a highly addictive substance with a short half-life, which can be injected, smoked, or nasally inhaled. Commonly prescribed opioids such as codeine, fentanyl, morphine, methadone, oxycodone, and hydrocodone are the most burgeoning drugs of abuse in the United States.[4,7] Although the usual route of administration of these medications is oral, they are also injected, nasally inhaled, smoked, used as dermal patches, or used as suppositories.[4] All of these agents have the potential for overdose, abuse, addiction, and physical dependence.

The continued use of illicit opioids and the associated lifestyle represents the greatest threat to the well-being of the mother, fetus, and neonate.[8] Severe opioid withdrawal can lead to fetal death because of the offspring's experience of acute opioid abstinence syndrome.[4] Untreated heroin use is associated with an increased risk of fetal growth restriction, abruptio placenta, fetal death, preterm labor, and intrauterine passage of meconium.[3] Compared with nonusers, heroin abuse increases the risk of a mother having a low birth weight neonate 4.6-fold.[3]

Infants exposed to opioids in utero also are at risk of developing neonatal abstinence syndrome (NAS). NAS is categorized by increased central nervous system excitability, and in many cases results in the need for pharmacologic withdrawal treatment.[8] Methadone and buprenorphine can be used to treat opioid cravings and withdrawals to help women abstain from using heroin. Although methadone has traditionally been the standard of care, newer data demonstrate the safety of buprenorphine use during pregnancy. The risk of NAS and hospitalization stay after birth is lower for infants exposed to buprenorphine than to methadone.[9,10] Buprenorphine has also been associated with higher birth weight in comparison with methadone.[10] The data comparing infants exposed to methadone with unexposed infants is mixed, with some studies demonstrating an increased risk of low birth weight and others demonstrating no difference.[3,11]

Cocaine

Cocaine blocks the presynaptic reuptake of the sympathomimetic neurotransmitters such as norepinephrine, serotonin, and dopamine, resulting in hypertension, tachycardia, and even cardiac arrhythmias.[12] Because of its sympathomimetic vasoconstrictive effects and resultant hypertension in both the mother and the fetus, placental infarcts and hemorrhage can occur at any time during pregnancy.[6] Cocaine exposure during pregnancy directly alters the uteroplacental blood flow, resulting in fetal and neonatal sequelae. Cocaine crosses the placental barrier easily, with amniotic fluid acting as a reservoir for fetal cocaine exposure. The overall malformation rate in pregnancies exposed to cocaine is around 10%.[4] Perinatal cocaine use has been associated with preterm birth, low birth weight, and small for gestational age (SGA) infants.[6] Nonetheless, some of the perinatal adverse effects commonly attributed to cocaine may be caused by confounders associated with its use.[13]

No pharmacologic substitutes have been identified for the effective treatment of stimulant abuse. The Cochrane Database reviews have evaluated antidepressants, anticonvulsants, and dopamine agonist agents for cocaine dependence, and have not shown benefit to derive from any such therapies.[14]

Amphetamines

In the United States it is estimated that 5% of pregnant women have used methampetamines.[1] In animal models, methamphetamines have been found to decrease uterine blood flow, increase uterine vascular resistance, and increase fetal blood pressure in dose-related fashion.[1] Amphetamine and its derivatives, methamphetamine and methylenedioxymethamphetamine (MDMA), are slowly metabolized and easily distributed to the central nervous system. Of note, amphetamine derivatives have longer half-lives and have more sympathomimetic properties than cocaine. After exposure to amphetamines, the elevated levels of circulating neurotransmitters (norepinephrine and serotonin) produce marked vasoconstriction and lead to adverse perinatal effects.[1] Amphetamine exposure in pregnancy is associated with higher unadjusted odds of preterm birth, low birth weight, and SGA neonates.[1]

Alcohol

Prenatal alcohol exposure has been reported by 12.5% of pregnant women, with 1.6% reporting frequent use of alcohol while pregnant.[15] Binge drinking ($\geq$4 drinks per occasion) has been estimated at 1.4% among pregnant women and 15% among nonpregnant women in the United States during the period 2006 to 2010. Factors related to maternal alcohol consumption during pregnancy and preconception binge drinking include maternal age, whether the pregnancy was planned, abuse of other

substances, marital status, history of physical and emotional abuse, mental health, self-esteem, prenatal care, nutrition, and socioeconomic status.[16] Regarding morbidity and mortality related to alcohol exposure, excessive alcohol consumption is the third leading preventable cause of death in the United States, and is estimated to be responsible for approximately 80,000 deaths annually. Alcohol can be a significant contributing factor to medical conditions such as hepatitis, hypertension, tuberculosis, pneumonia, pancreatitis, and cardiomyopathy.[17] Fifty percent of all cases of cirrhosis in the United States have been found to be due to alcohol-use disorders. Excessive alcohol consumption also contributes to cancers of the mouth, esophagus, pharynx, larynx, and breast. Alcohol abuse inflicts central nervous system disease including dementia, stroke, and peripheral nervous system disease such as neuropathy and myopathy.[18]

Prenatal alcohol exposure has been found to be a risk factor for fetal mortality, stillbirth, and infant and child mortality. One or 2 hours after maternal ingestion, the fetal blood alcohol concentrations reach levels nearly equivalent to maternal levels.[15] Fetal exposure time is prolonged, arising from reuptake by the fetus of the amniotic fluid containing ethanol. Fetal alcohol exposure increases the risk of extreme preterm delivery.[19] Research has also found that alcohol consumption during pregnancy increases the risk of fetal death.

ANTEPARTUM FETAL EVALUATION OF WOMEN USING ILLICIT DRUGS

The goal of antepartum fetal evaluation is to decrease perinatal mortality and permanent neurologic injury through judicious use of reliable and valid methods of fetal assessment (**Fig. 1**).[20,21]

Women with increased risk for stillbirth should undergo antepartum fetal surveillance using a nonstress test (NST), contraction stress test (CST), biophysical profile (BPP), or modified BPP. Initiating this testing at 32 weeks of gestation is appropriate

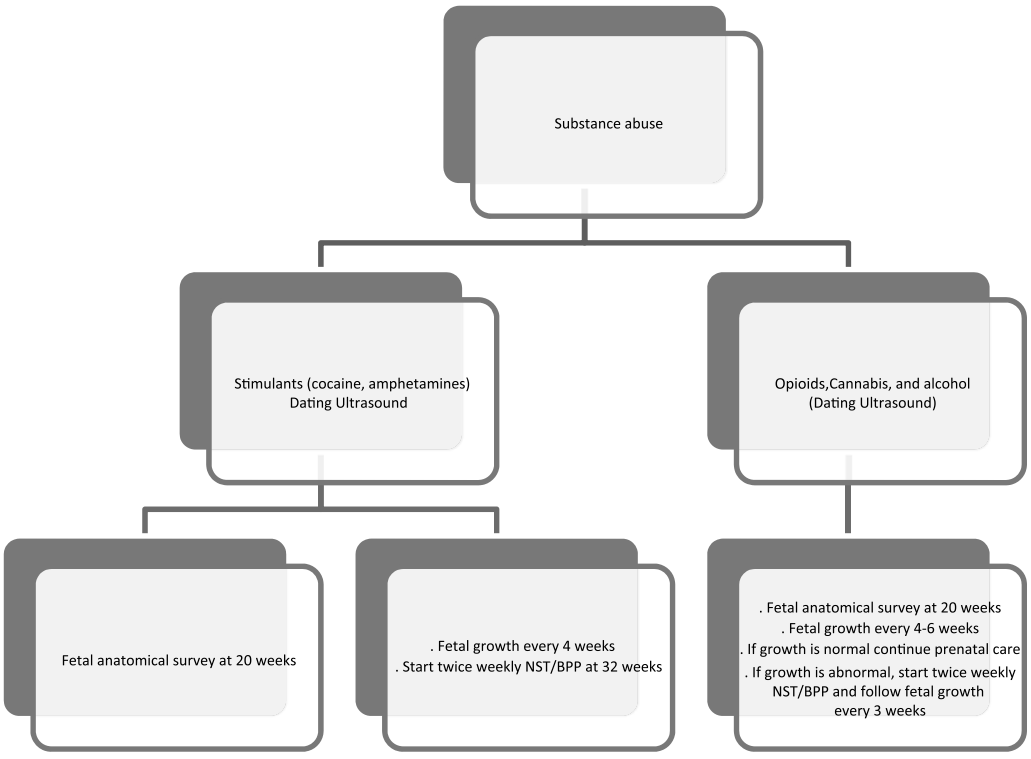

Fig. 1. Antepartum testing scheme. BPP, biophysical profile; NST, nonstress test.

for most pregnancies at an increased risk of stillbirth.[21] In all these testing schemes, the prevalence of the abnormal condition will have a great impact on the predictive value of the antenatal tests and the number needed to evaluate with testing and to treat with interventions; that is, delivery to presumably prevent fetal death.[20]

Several tests are available to engage in close surveillance of patients at risk. Fetal movements or kick counts is a more indirect indicator of fetal oxygenation, because decreased fetal movements occur in response to hypoxemia. Studies performed to assess fetal movement counts have failed to conclusively show benefits in the prevention of perinatal mortality.[20,21] The NST is based on the premise that the heart rate of the fetus that is not acidotic or neurologically depressed will temporarily accelerate with fetal movement.[21] Fetal heart rate reactivity is thought to be a good indicator of normal fetal autonomic function, whereas loss or reactivity is associated most commonly with a fetal sleep cycle, but it may result from any cause of central nervous system depression including fetal acidosis.[20,21]

The CST, or oxytocin challenge test, is based on the fact the uterine contractions produce reductions in the blood flow in the intervillous space. An inadequate placenta respiratory reserve would demonstrate recurrent late decelerations in response to hypoxia.[20,21]

The BPP consists of an NST combined with 4 observations made by real-time ultrasonography. The 5 components are the NST, the fetal breathing movements, the fetal movements, the fetal tone, and the determination of the amniotic fluid volume.[21] The BPP correlates well with a fetal acid-base status. A modified BPP is based on the fact that the amniotic fluid reflects fetal urine production. If there is placental dysfunction, this may result in diminished fetal renal profusion, leading to oligohydramnios. Amniotic fluid volume can therefore be used to evaluate long-term uteroplacental dysfunction. As discussed earlier, the NST is a short-term indicator of the fetal acid-base status when combined with the amniotic fluid index (AFI), which is the sum of measurements of the deepest cord-free amniotic fluid pocket in each abdominal quadrant; these 2 tests serve as an indicator of long-term placental function.[21]

It is also important to mention the use of ultrasonography in women involved with substance abuse. Ultrasonography can be used to diagnose many major fetal anomalies. Prenatal ultrasonography may reduce the rate of perinatal mortality, primarily through pregnancy termination for prenatal diagnosed congenital anomalies, but does not appear to reduce the rate of perinatal morbidity. Ultrasonography also provides a more accurate estimation of gestational age, which prevents unnecessary labor induction for postterm pregnancy.[22] Ultrasonographic examination between 18 and 20 weeks of gestation allows for a reasonable survey of fetal anatomy and an accurate estimation of gestational age. Therefore, the optimal timing for a single ultrasonogram is between 18 and 20 weeks, because anatomically complex organs such as the fetal heart and brain can be imaged with sufficient clarity to allow detection of many major malformations at a time when termination of pregnancy may still be an option. Other uses of ultrasonography during pregnancy are the evaluation of cervical length, determination of gestational age, evaluation of amniotic fluid, detection of disturbances of fetal growth, and detection of chromosomal abnormalities in the second trimester.[22]

ANTEPARTUM TESTING GUIDELINES FOR PATIENTS WITH SUBSTANCE ABUSE

Because of the high incidence of low birth weight, fetal anomalies, preterm delivery, and growth restriction, the authors recommend obtaining an ultrasonogram for appropriate pregnancy dating, a detailed anatomic survey, and cervical length at 20 weeks

of gestation. The authors also perform urine drug screens during every clinic visit to assess whether these patients are using or abusing other substances.

Pregnant women with active substance abuse can be cared for in specialized prenatal clinics designed to care for women with addiction, or by individual prenatal providers with experience in addiction medicine. At the time women establish care, an initial ultrasonogram for assessment of gestational age is recommended. These patients may also be offered the opportunity for aneuploidy screening in the first and second trimester. An anatomic survey of the fetus is obtained at 20 weeks. The progress of the pregnancy is assessed by frequent prenatal visits and fundal height.

If there is sufficient discrepancy in the growth to suspect macrosomia or growth restriction, ultrasonography is repeated. Women in the authors' specialized substance-abuse prenatal clinic have a higher incidence of intrauterine growth restriction in comparison with other women delivering at the institution. Although it is unclear whether this finding is due to active substance abuse, opioid substitution therapy, or confounders such as tobacco abuse and poor weight gain, growth ultrasonograms on women at 28 and 34 weeks' gestation are routinely obtained to screen for intrauterine growth restriction. The authors do not routinely perform antenatal testing in this population. If a fetal growth disorder is identified, the mother is followed with twice-weekly NSTs starting at 32 weeks, and weekly AFIs or modified BPPs.

In patients who are abusing stimulants such as methamphetamines and cocaine, fetal growth is followed every 3 to 4 weeks. Because of the generalized vasoconstriction that these patients develop, antenatal testing is started routinely at 32 weeks with twice-weekly NSTs and a once-weekly modified BPP. Also of importance is that opioid substitution therapy affects fetal assessment by NST and BPP. A decrease in fetal heart rate can be found in opioid-dependent mothers as early as the first trimester.[23] After methadone administration, the reactivity of NSTs decreases.[24] The baseline heart rate is also slower, with fewer accelerations and decreased variability.[8] Buprenorphine, compared with methadone, is less likely to have these effects.[25]

Intrapartum Management

In women with active stimulant abuse, the authors routinely induce labor at 38 weeks of gestation because of the increased risk of abruptio placenta, balancing this risk with the risk of prematurity. Owing to this higher incidence of abruptio placenta secondary to cocaine and methamphetamine abuse, it is recommended that women using stimulants be placed on continuous fetal monitoring and be observed for hypertonic contractions. The limited use of short-acting benzodiazepines is allowed for symptomatic relief of severe agitation from stimulant withdrawal, if needed, during inpatient care.[9,14,26]

As with antepartum interpretation of NSTs, methadone also affects intrapartum fetal heart rate patterns, with a decreased fetal heart rate baseline, fewer accelerations, and decreased variability.[27–30] Women receiving opioid substitution therapy undergoing labor should receive routine pain relief as if they were not taking opioids, because the maintenance dose does not provide adequate analgesia for labor.[4] Epidural or spinal anesthesia should be offered, where appropriate, for management of pain in labor or for delivery. Narcotic agonist-antagonist drugs such as butorphanol and nalbuphine should be avoided because they may precipitate an acute opioid withdrawal.[4] As a general rule, patients undergoing opioid maintenance treatment will require higher dosages of opioids to achieve an analgesic effect in comparison with other patients.[4] The authors do not stop buprenorphine therapy in labor or for cesarean sections. Instead, the dose of buprenorphine is divided 3 to 4 times throughout the day to improve its analgesic effect, and the dose of the other opioids given for pain control is increased.

SUMMARY

This article addresses the effects of illegal and legal substance abuse on both mother and fetus, and discusses the antepartum and intrapartum management of substance-abusing patients. When assessing the impact of illicit drug exposure on pregnancy, clinicians are confronted with several common confounders, including tobacco use, limited use of and access to prenatal care, polysubstance exposure, lack of insurance coverage, low socioeconomic status, and improper nutrition.[1] The evidence presented suggests that exposure to substance abuse during pregnancy has a negative effect on the birth weight, gestational age at delivery, fetal growth, and the possibility of abruptio placenta. Once identified, these patients should ideally attend a specialized clinic where comprehensive care of perinatal substance abuse can be provided. These specialized clinics can improve maternal and perinatal outcomes. Not only is the fetus placed at risk in these situations but the mother is also at risk for hypertensive disorders, cardiovascular fluctuations, and placental abruption, as well as maternal mortality in some situations.

There is evidence that perinatal outcomes improve in some of the monitored populations who undergo fetal assessment.[7] The American College of Obstetricians and Gynecologists suggest starting fetal monitoring at between 32 and 34 weeks. However, fetal testing should be individualized according to which high-risk disorder affects the fetus.[7,21] At the authors' institution, antepartum testing protocols for the substance abuse population are started at 32 weeks of gestation. In those cases presenting with evidence of growth restriction before 32 weeks it is recommended that testing protocols should begin earlier, around 28 weeks' gestation.

Antepartum complications, such as substance abuse, can lead to uteroplacental insufficiency and intrapartum events that can result in adverse neonatal outcomes. The labor of women with such high-risk conditions should be monitored with continuous fetal heart rate monitoring. In these circumstances a 3-tiered system for the categorizations of fetal heart rate patterns is recommended.[11]

In essence, clinicians need to make their best effort to identify patients with substance addictions and thus be able to provide adequate maternal and fetal care.

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