Effect of Maternal Substance Abuse on the Fetus, Neonate, and Child

Nicole A. Bailey, MD,*† Magaly Diaz-Barbosa, MD*†

*Division of Neonatology, Kidz Medical Services, Coral Gables, FL

†Division of Neonatology, Nicklaus Children's Hospital/Florida International University School of Medicine, Miami, FL

Practice Gap

Clinicians should be able to describe the short- and long-term effects on the newborn of exposure to substance abuse in utero.

Objectives

After completing this article, readers should be able to:

1. Describe the placental transfer of drugs and their effect on embryogenesis.
2. Identify the methods to screen for drugs in the mother and neonate.
3. Understand the short- and long-term adverse effects of legal and illicit maternal substance abuse in the newborn.
4. Identify therapies for the drug-exposed neonate.
5. Describe American Academy of Pediatrics recommendations for breastfeeding mothers who abuse substances.

AUTHOR DISCLOSURE Drs Bailey and Diaz-Barbosa have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
ACOG	American College of Obstetricians and Gynecologists
ADHD	attention-deficit/hyperactivity disorder
AMPH	amphetamine
CNS	central nervous system
FAS	fetal alcohol syndrome
LBW	low birthweight
MDMA	3,4-methylene-dioxymethamphetamine
METH	methamphetamine
NAS	neonatal abstinence syndrome
NIDA	National Institute on Drug Abuse
PCP	phencyclidine
SSRI	selective serotonin reuptake inhibitor

INTRODUCTION

The abuse of certain drugs or medications during pregnancy can have detrimental effects on the fetus and neonate. Previous research has shown that 5% of pregnant women use 1 or more addictive substances. (1)(2) Approximately 1 in 20 infants is exposed to illicit drugs. (3) Marijuana, cocaine, heroin, hallucinogens, and inhalants are examples of illicit drugs. (4) According to a 2010 survey conducted by the National Institute on Drug Abuse (NIDA), 16% of pregnant women aged 15 to 17 years, 7.4% of pregnant women aged 18 to 25 years, and 1.9% of pregnant women aged 26 to 44 years abuse illicit substances. (5) From 2002 through 2010, the rate of reported illicit drug use among pregnant women aged 15 to 44 years rose from 3% to 4.4%. (1)(5)(6) The maternal abuse of narcotics has also risen because of "more liberal use of prescription opiates in pregnant women to palliate acute and/or chronic pain." (7) As a result, the incidence of infants born addicted to drugs has increased. (1) The rise in substance use disorders among pregnant women is an alarming public health concern because the abuse of these medications poses a health risk to the fetus, the neonate, and the developing child.

Likewise, maternal abuse of legal substances such as alcohol, caffeine, nicotine, and even nonmedical use of prescription drugs during pregnancy is also

concerning. Approximately 10% of infants are exposed to alcohol in utero, and 20% are exposed to nicotine. (3) In addition, pregnant women may expose their fetuses to other legal medications (ie, nonsteroidal anti-inflammatory drugs, salicylates, angiotensin-converting enzyme inhibitors, warfarin, and others) that are not known to have abusive potential but that are known to adversely affect the fetus. (3) Thus, "legality of a substance does not necessarily correlate with its safety profile." (4) These substances, whether illicit or licit, can have long-lasting effects beyond the neonatal period. However, the true incidence of maternal abuse of addictive, commonly used, and/or prescribed substances may never be truly known as substance abuse is frequently underreported. (1)

The purpose of this article is to report trends in prenatal substance abuse, to describe how the fetus is affected in utero, to review methods to test for drug abuse in utero, and to describe licit and illicit drugs of abuse during pregnancy. Treatment of exposed neonates will also be reviewed. This article ultimately serves to update current knowledge of short- and long-term outcomes of drug-exposed neonates with the goal of equipping pediatricians to fulfill their role as lifelong health care advocates to babies, children, and young adults.

PLACENTAL TRANSFER OF DRUGS

The human placenta serves to regulate the flow of substances and nutrients from the mother to the fetus. Medications, drugs, and their metabolites can easily enter fetal circulation from the placenta. Some factors that affect this placental transfer depend on the specific drug, the concentrations of the drug in the maternal and fetal circulations, the method and timing of administration, the genetic makeup of both the mother and the fetus, and the co-administration of other drugs. (8)(9) "Other factors important to drug transfer across the placenta include differences between the maternal and fetal osmotic pressures and pH, as well as changes in the uterine or placental blood flow." (8) Cocaine, heroin, nicotine, and marijuana can affect placental blood flow through vasoconstriction. The other factors that regulate placental drug transfer include high lipid solubility, an unionized drug form, low molecular weight (<5000 Da), and low protein binding. (8) The adverse effects of in utero exposure to drugs can lead to abnormalities in breathing, intrauterine growth restriction, and possibly fetal death. A fetal withdrawal syndrome has been reported in which the abrupt cessation of opiates in utero can lead to premature delivery, low birthweight (LBW), and even stillbirth. (9)

MATERNAL DRUG USE AND ITS EFFECTS ON EMBRYOGENESIS

Structural abnormalities or teratogenicity may also result from in utero drug exposure. The timing of drug exposure in utero determines the effect. (8) One possible adverse effect of any abused drug during the first week of pregnancy is miscarriage. The incidence of this complication is unknown because it may be difficult to determine the exact date of conception and exclude other factors that would cause termination of the pregnancy. It is well known that nearly all drugs of abuse have been associated with preterm birth. (3)

The second to eighth weeks of pregnancy compose the period of organogenesis, when drugs can produce structural abnormalities at the cellular level or interfere with growth of the developing fetus. (3)(8) Barbiturates during pregnancy have been noted to cause dysmorphic features. There is evidence for remodeling of vessels in the heart associated with selective serotonin reuptake inhibitor (SSRI) use during pregnancy. Alcohol, for instance, can produce structural abnormalities that lead to fetal alcohol syndrome (FAS). Prenatal alcohol intake can also cause fetal growth restriction. Likewise, heroin, methadone, nicotine, and cocaine have also been implicated in interfering with fetal growth. However, these effects on fetal growth may also be multifactorial because these abused substances are also known to reduce maternal appetite, can affect placental blood flow, and are sometimes used by women in lower socioeconomic groups with limited and disrupted resources. (8)

By the third month of pregnancy, the differentiation of the central nervous system (CNS) begins and is not completed until after birth. Thus, birth is not an end point, but a developmental milestone. (8) Some addictive drugs that are known to affect the developing CNS are opioids, marijuana, cocaine, and methamphetamine (METH). (3) In addition, in utero exposure to many antiepileptic drugs has been shown to increase the risk of cognitive and behavioral impairments in childhood as a result of widespread neuronal apoptosis in the developing brain. (10)

Although the adverse effects of many drugs on a developing fetus are known, sometimes it is difficult for a pregnant mother to abruptly discontinue a drug. Some mothers may depend on medications for medical reasons. Others may depend on medications such as methadone to prevent drug relapse during pregnancy. The safety of both the mother and the fetus must be considered in the decision to discontinue a medication. "Any drug taken during pregnancy must be considered to be potentially harmful to the fetus, and the risk versus the benefits of its use should be assessed carefully." (8)

DIAGNOSING MATERNAL DRUG ABUSE

In 2003, the Child Abuse Prevention and Treatment Act was revised by the US Congress when they passed the Keeping Children and Families Safe Act. (11) This law empowered individual states to implement a plan for newborns exposed to illicit substances. However, "the Act [left] the decision on who should be tested to the healthcare provider." (11) In 2017, the American College of Obstetricians and Gynecologists (ACOG) recommended universal substance abuse screening during the first prenatal visit for all women regardless of ethnicity, socioeconomic background, poor adherence to prenatal care, or previous adverse pregnancy outcome. (12) Routine screening for substance abuse disorders involves having a brief conversation with the patient and using validated screening tools such as questionnaires. (12)

Most hospitals will perform a drug test on a mother and/or her infant for placental abruption, a history of maternal drug use, repeated spontaneous abortions, cerebrovascular accidents, and hypertensive episodes if there is a concern that any parent is under the influence of a substance, if there is a history of absent or inadequate prenatal care, or if there is a clinical concern for drug withdrawal in the neonate. (7) However, the ACOG recommends that drug testing on a mother be performed in compliance with state laws, only after obtaining a patient's consent, and after informing the mother of potential consequences resulting from a positive test result. (12)(13) Several state governments do have policies to prosecute and incarcerate pregnant women with substance use disorders. (13)(14) However, "this approach has no proven benefits to the mother-infant dyad." (14)

Immunoassays "have been used widely for mass drug screening, with positive samples confirmed by more specific techniques, such as high-performance liquid chromatography and gas chromatography–mass spectrometry." (15) Drug testing can be performed on urine, blood, meconium, hair, or umbilical cord blood or tissue samples, but there is no gold standard. (6)(11) Urine is usually the most noninvasive sample to obtain in a newborn and mother. However, urine has its limitations. Urine toxicology may not detect synthetic opioids, some benzodiazepines, and some designer drugs. (12) The clearance of drugs from urine is very rapid, occurring only within hours to several days after consumption. (12)(15) In addition, urine toxicology tests "provide objective evidence of drug use at one point in time and do not enable providers to determine the frequency of use or degree of use." (14) Meconium is formed in the second trimester and is a composite of all substances that reach the fetal circulation. It reflects drug exposure in the last several weeks to months preceding delivery. Meconium drug screening has higher sensitivity compared with urine specimens (11)(15) and is indicative of long-term drug use. Although a negative urine screen taken with a positive meconium screen may reflect previous use of a substance, a positive urine screen with a negative meconium test result may indicate recent drug use that has not had time to accumulate in the meconium. One limitation of meconium drug screening is delayed detection of maternal drug use in babies who are not passing meconium, which is often seen in premature babies and critically ill babies who are not being fed.

Testing of hair samples as a toxicological screening matrix has been around for decades. (15) A positive hair sample in a neonate indicates third trimester use. However, its use is limited in neonates because only a handful of laboratories can process these specimens, and obtaining a sufficient sample may be difficult for some newborns with very little hair. (15) Maternal or neonatal blood collection is also another option. However, the test is invasive and would reflect recent use only. Umbilical cord blood collection was "shown to perform as well as meconium in assessing fetal exposure to various drugs." (16) However, it is not commonly used due to a narrow time frame to collect cord blood and an unsettled time frame of drug use in the mother. Tissue sample collection, ie, neonatal fingernail, is another option. It would indicate fetal exposure from mid-gestation. (15) There has been little published to substantiate this form of testing other than in case reports.

Substances that are commonly tested for in drug screens are metabolites of marijuana, cocaine, sedatives (ie, barbiturates and benzodiazepines), narcotics (ie, opioids), amphetamines (AMPH), and, less commonly, nicotine. Alcohol may not be included on all drug screens because of "low immunoassay sensitivity for ethanol and the agent's short circulation." (15) Health care professionals may rely on maternal self-report or screening tools to detect abuse of nicotine or alcohol in pregnant women. Sometimes, mothers self-report passive exposure to illicit drugs after a drug screen result is positive. "Passive exposure to heavy amounts of second-hand marijuana or crack cocaine smoke in an adult can result in a positive drug test, but low levels typically do not." (11) In addition to objective tests such as drug screening, several semi-objective tools, such as the modified Finnegan Neonatal Abstinence Scoring Tool, are available to assess a neonate's prenatal exposure to opioids. These tools will be addressed in a separate section.

COMMONLY CONSUMED ADDICTIVE SUBSTANCES

Caffeine

One of the most common addictive, but legal, substances consumed during pregnancy is caffeine. It is a naturally

occurring stimulant found in many products, such as tea, coffee, sodas, cocoa, and chocolate. "Caffeine has been detected in amniotic fluid, umbilical cord, urine, and plasma of fetuses, which suggests that caffeine is easily transmitted across the placenta." (17) Although considered to be a fairly harmless substance, studies have shown that pregnant women have slower caffeine metabolism compared with nonpregnant women and that fetuses have immature livers that produce a low level of the enzyme necessary for caffeine metabolism. (17) As a result, newborns exposed to caffeine in utero are at risk for jitteriness, bradycardia, emesis, and tachypnea, which can present at birth and last up to 1 week of age. (7) Other adverse effects that have been reported include miscarriage, preterm delivery, and LBW. (17)(18) It is well known that LBW infants are at risk for obesity, diabetes, and hypertension in adulthood according to the Barker hypothesis. Nonetheless, due to the reported adverse outcomes related to caffeine consumption during pregnancy, the ACOG issued a statement in 2010 advocating for moderate caffeine consumption (<200 mg/d) during pregnancy. (18) The ACOG states that "moderate caffeine consumption does not appear to be a major contributing factor in miscarriage or preterm birth and that the relationship of caffeine to growth restriction remains undetermined." (18)

Nicotine

The most commonly abused substance during pregnancy is nicotine. According to the NIDA, 20% of pregnant women continue to smoke throughout pregnancy. (5) More than 7,000 chemicals that are toxic, carcinogenic, and/or teratogenic can be found in cigarette smoke. (4) Just like caffeine, nicotine easily crosses the placenta, which can expose the fetus to nicotine concentrations that are 15% higher than in maternal blood. (3) In addition to maternal use of cigarettes, a fetus can also be exposed to nicotine through second-hand smoke and through nicotine replacement therapies (ie, gum, lozenges, patches, e-cigarettes), which are equally detrimental to the health of the fetus. (4)(19)(20)

Nicotine has been shown to interfere with oxygen delivery, thus affecting growth of the fetus in utero. Dose-dependent LBW and preterm birth has been associated with prenatal exposure to nicotine. (3)(19)(20) Prenatal use of nicotine also places the fetus at risk for intrauterine death. (9) It has also been described as a "neuroteratogen that comprises critical neural pathways in the developing brain." (3) Reports of sporadic congenital anomalies associated with nicotine have shown an increased incidence "of orofacial clefts, neural tube defects, and cryptorchidism, although large-scale studies have no significant increase in gross malformations." (3)

Postnatally, babies heavily exposed to nicotine in utero are at increased risk for poor arousal, irritability and hyperexcitability, hypertonicity, and tremors. (3)(9) Within the first several months of life, nicotine-exposed infants exhibit signs of poorer self-control, more negative affect, distress in response to limitations, and decreased soothability. (4)(9)(21) There is also an association with sudden infant death syndrome with prenatal and postnatal use of tobacco. Long-term, into childhood and even young adulthood, they demonstrate cognitive deficits and a diminished response to auditory stimuli, an effect that can lead to learning and language disabilities, which can cause poor academic achievement in school. (4) "Prenatal nicotine exposure has been consistently associated with lower IQ throughout childhood." (9) Exposed children as young as 6 years of age are at higher risk for attention deficits, depression, anxiety, and conduct disorders. Interestingly, there was no difference in long-term cognitive outcome between babies exposed to tobacco during the entire pregnancy and those exposed only during the first trimester. This finding emphasizes the need for smoking cessation before pregnancy. (4) "Prenatal tobacco exposure appears to increase the likelihood of tobacco use in childhood and early adolescence." (9) In addition, similar to caffeine, prenatal exposure to nicotine increases the risk of adult disease owing to its association with LBW.

Alcohol

The second most common substance of abuse during pregnancy is alcohol. According to the NIDA, females aged 15 to 44 years reported alcohol consumption during pregnancy slightly greater than 15% and binge drinking during pregnancy at a rate of less than 15%. (5) "Binge drinking is defined as drinking 4 or more drinks on the same occasion on at least 1 day in the past 30 days." (1) In addition, "1% of pregnant women report heavy drinking, defined as drinking 1 or more drinks each day." (1) Because there is no safe limit of alcohol intake for pregnant women or for women of reproductive age who are trying to become pregnant, the recommendation by the ACOG is for such women to abstain from alcohol. (22)

Similar to nicotine, alcohol easily crosses the placenta and can be identified in maternal and fetal blood as well as in amniotic fluid. (6) Alcohol is believed to affect the developing fetus during the embryonic and fetal stages of development. (6) It is also hypothesized that alcohol affects vascular tone in the umbilical vessels through decreased placental blood flow, which may predispose the fetus to hypoxia, causing LBW. (6) In addition to LBW, preterm birth is another short-term complication of maternal alcohol use in utero. A neonatal alcohol withdrawal phenomenon has been described as abdominal distention, excessive mouth movements,

jitteriness, irritability, seizures, opisthotonus, and reflex abnormalities in newborns exposed to alcohol in utero. (3)(7) Withdrawal from alcohol can occur several hours after delivery. Duration of signs could last up to 18 months of age. (7)

Long-term complications of prenatal alcohol use are encompassed by the well-described but preventable FAS, which is "characterized by specific facial features, growth deficiency, central nervous system abnormalities, behavioral abnormalities, and intellectual disability." (3) It is estimated that 0.2 to 1.5 infants for every 1,000 live births are affected with FAS. (1)(23) Prenatally alcohol-exposed adolescents and young adults demonstrate learning problems, attention disorders, and cognitive impairments. They are at risk for impulsivity, irritability, inappropriate sexual behavior, criminal activities, depression, and suicidal tendencies. In addition, "prenatal alcohol exposure appears to be a risk factor for alcohol abuse in young adulthood, even after controlling for other relevant covariates." (8)

Opioids

Patients may be prescribed opioids during pregnancy for chronic pain or addiction, opioid misuse, and an untreated opioid use disorder. (12) Prescription drug abuse of narcotics has become a growing concern that affects people of all ages, socioeconomic classes, and locations in this country. It is estimated that between 2000 and 2009, the incidence of opioid-exposed newborns with withdrawal symptoms, also known as neonatal abstinence syndrome (NAS), increased from 1.2 per 1,000 hospital births per year to 3.39 per 1,000 hospital births per year. (24)(25)(26) Neonates exposed to opioids in utero are at increased risk for LBW, microcephaly, NICU admissions, and a prolonged hospital stay compared with nonexposed babies. (1)(24) The average length of stay for opioid-exposed babies is 17 days, and 23 days for those requiring medication. (27) Prenatal exposure to opioids also significantly increases the risk of preeclampsia, stillbirth, prematurity, and sudden infant death syndrome. (1)(12) An association between prenatal opioid use and congenital malformations such as congenital heart disease, gastroschisis, and spina bifida has been suggested. (1)(4)(28) However, a recent systematic review of case-control and cohort studies on this subject was unable to confirm this claim. (29)

The most common postnatal complication of in utero opioid exposure is the development of withdrawal symptoms, first described in the early 1900s as *congenital morphinism*. (30) By the 1970s, congenital morphinism had been renamed NAS by Dr Loretta Finnegan. (27) "Although other drugs such as benzodiazepines, amphetamines, cocaine, and barbiturates can produce NAS, studies show that it is highest among opioid-exposed babies." (1) As a result of NAS, neonates experience problems related to the nervous system, respiratory system, gastrointestinal system, and other regulatory systems. (1) On physical examination, these babies may exhibit abnormal tone, temperature instability, poor feeding, poor suck, difficulty sleeping, seizures, inconsolability, sneezing, stuffiness, high-pitched cry, and tachypnea. (9)(31) Signs and symptoms of NAS occur in 50% to 95% of opioid-exposed infants. (1)(27) Most infants will present with symptoms by 2 to 3 days of age. However, the onset of symptoms may be up to 1 to 2 weeks of age. The American Academy of Pediatrics (AAP) recommends that "a neonate born to a mother on an opioid with a short half-life be observed in the hospital for at least 3 days if there are no signs of withdrawal and that an infant born to a mother on an opioid with a long half-life be observed in the hospital for a minimum of 5 to 7 days." (7)

Currently, the modified Finnegan Neonatal Abstinence Scoring Tool is the most prevalent tool in the United States to assess for opioid withdrawal in a term or near-term neonate with withdrawal symptoms. (7) "Preterm babies are at lower risk for experiencing drug withdrawal and have less severe and/or shorter courses of withdrawal which may be related to CNS immaturity, differences in total drug exposure, or lower fat depots of drug." (7) This tool assigns a score based on CNS disturbances, vasomotor and respiratory disturbances, and gastrointestinal disturbances that are commonly associated with opioid withdrawal. The neonate is assessed every 3 to 4 hours 30 minutes to 1 hour after a feeding during his or her hospitalization. "Opioid agonist pharmacotherapy is recommended for infants who have modified Finnegan scores above a threshold level." (3) Treatment of NAS will be further addressed in a separate section.

"At the pre- and elementary school ages, opioid-exposed children show motor and cognitive impairments, inattention, hyperactivity, and increase in attention deficit disorders." (4) "Prenatal opiate exposure has also been associated with behavioral problems in childhood." (9) One study found that infants with a diagnosis of NAS are at greater risk for child abuse and for placement in a foster home. (32) Longer-term, there are very little data accounting for performance in adolescents with a diagnosis of NAS at birth. However, 1 Australian study that evaluated children with a diagnosis of NAS in grades 3 through 7 reported poor and deteriorating school performance in this population of children. (33)

MATERNAL ILLICIT SUBSTANCE ABUSE

Hallucinogens

Recent literature is lacking on the effect of phencyclidine (PCP), lysergic acid diethylamide (LSD), and other

hallucinogens on the fetus and neonate. The exact incidence of hallucinogen use during pregnancy is unknown. However, research from the 1980s and 1990s suggests that neonates exposed in utero to hallucinogens are at increased risk for microcephaly and alterations in facial features. (3) Neurobehavioral symptoms in PCP-exposed neonates include "decreased attention, high pitched cry, poor visual tracking, tremors, lethargy, nystagmus, poor feeding, and altered reflexes." (3) Longitudinal studies that follow the neurodevelopment of these neonates into childhood are currently not available.

Inhalants

Inhalant abuse (or volatile substance misuse) involves an intentional or occupational overexposure to chemicals and gases such as fuels, solvents, propellants, glues, adhesives, and paint thinners that produce an alcohol-like intoxication. "Inhalants are legal, inexpensive and easy to obtain, all of which may account for the higher abuse potential among younger individuals." (34). The incidence, teratogenic effects, and long-term sequelae of prenatal inhalant exposure remain understudied at this time. However, previous reports suggest that overexposure to inhalants during pregnancy can increase the risks of preeclampsia, spontaneous abortion, fetal malformations, adverse neurodevelopmental outcome in the newborn, and fetal solvent syndrome, which manifests as LBW, microcephaly, facial dysmorphology, and muscle tone abnormalities similar to those occurring in FAS. (35) It is also suggested that infants prenatally exposed to inhalants are at increased risk for an alcohol-like withdrawal phenomenon in the newborn period. (35)

Marijuana

Marijuana remains an illegal substance under federal law. However, with the legalization of marijuana for recreational and/or medicinal purposes in several US states, the increase in its use among pregnant women is a growing concern. Recent statistics have shown that the prevalence of recent marijuana use among pregnant women increased 62% from 2002 through 2014. (36) "Marijuana elicits a sedative-like effect in the mother primarily due to its active ingredient tetrahydrocannabinol (THC) and can remain in the body for up to one month, thus lengthening fetal exposure to the drug." (6) However, "unlike other drugs, the placenta appears to limit fetal exposure to marijuana as fetal marijuana metabolite levels have been documented to be lower than maternal concentrations in animal studies." (6)

Overall, marijuana is the third most commonly abused drug during pregnancy. However, it is the most common illicit drug used during pregnancy. Fetal exposure to marijuana "does not cause clinically important neonatal withdrawal signs, but may have subtle effects on long term neurobehavioral outcomes." (7) Long-term, the IQ of marijuana-exposed children is not affected. However, studies in school-aged children and adolescents "reveal effects of prenatal exposure to marijuana on behavior, cognition, and achievement, but not on language and growth." (6) "At age 10, children who had been exposed to marijuana during the first and third trimester of pregnancy experience more symptoms of depression compared with controls." (9) In addition, prenatal marijuana exposure doubled the risk of marijuana use among 16- to 21-year-olds. (9) Short-term effects of prenatal marijuana exposure are neurobehavioral. Newborns exposed to marijuana can exhibit sleep disturbances, increased startle and tremors, and a high-pitched cry. (3)(4) There is minimal evidence to suggest that marijuana in utero causes prematurity, LBW, or congenital anomalies. The harmful effects of marijuana on the fetus are related to actions on the developing brain of the fetus, altered uterine blood flow, and altered maternal health behaviors. (3)(6)

Cocaine

Overall, cocaine is the fourth most common substance abused during pregnancy. Cocaine abuse affects at least 750,000 pregnancies per year. (37) Cocaine has sympathomimetic properties that can cause vasoconstriction, hypertension, tachycardia, and cardiac arrhythmias. As a result, cocaine use during pregnancy increases the risk of placental abruption, abortion, and premature birth, among other complications. As with any other substance, the most dangerous period of drug use is during organogenesis. (37) An increased risk of congenital malformations, especially of the brain and heart, has been suggested. Fetal brain growth, weight, and length are also restricted secondary to the vasoconstrictive effects of the drug. In addition, the fetus is also at risk for bowel infarction, atresia or perforations, porencephalic cysts, and nonsyndromic limb malformations. (37)

In the cocaine-exposed neonate, restricted fetal growth leads to LBW, microcephaly, and decreased length. (9)(38) Signs and symptoms of prenatal cocaine exposure manifest within the first 2 to 3 days of life. These symptoms include hyperalertness, excessive suck, jitteriness, high-pitched cry, irritability, and autonomic instability (ie, tachycardia, hypertension). (3)(38) Delivery room resuscitation, intubation, and NICU admissions occurred more frequently in cocaine-exposed babies. (38)

Long-term, "growth restriction among prenatal cocaine exposure children has been documented to continue past infancy and may persist in children up to 10 years of age."

(4) Although, recent studies have shown that children exposed to heavy cocaine in utero are at increased risk for higher body mass index and blood pressures compared with nonexposed children. (37) Although IQ is not necessarily affected, executive functions such as cognition, language skills, memory, problem-solving skills, attention, and behavior are affected. Exposed children were more likely to be in the custody of child protective services, a foster parent, or an adoptive parent. Little is known about the long-term adult health effects associated with in utero cocaine exposure. (37)

METH AND ITS METABOLITES

METH is "a member of a group of sympathomimetic drugs that stimulate the CNS." (6) 3,4-Methylenedioxymethamphetamine (MDMA) and AMPH are metabolites of METH. "According to the United Nations, 1.3% of the general population in Central and North America use amphetamine-type stimulants." (4) METH "readily passes through the placenta and blood-brain barrier and can have significant effects on the fetus and newborn." (6) One multicenter prospective longitudinal study on METH-exposed neonates suggested that prenatal METH use is associated with LBW. (39) Microcephaly and decreased length have also been associated with prenatal METH use, whereas other studies have demonstrated that when taken at therapeutic doses, METH has not been shown to have negative effects on the fetus or neonate. (9) Similar to cocaine, there is an increased risk of prematurity, placental abruption, (39)(40) and congenital malformations of the brain and heart. (4)(7) Unlike cocaine, METH-exposed newborns exhibit minimal symptoms, if any. Long-term, short stature and deficits in fine motor performance may exist during the first 3 years of life. (4)(7) At 3 and 5 years of age, METH-exposed babies are at risk for behavioral problems, depression, and attention-deficit/hyperactivity disorder (ADHD). (41) At almost 8 years of age, prenatal METH exposure is associated with increased cognitive delays. (42)

AMPH, also known as *speed*, is used either legally for the treatment of ADHD or for recreational purposes. It is not known how many women are using AMPH either legally or illegally during pregnancy. AMPH is not known to be teratogenic. (4) However, it is associated with a higher odds of prematurity and LBW. (4) Long-term, "it has been reported that AMPH causes an increased prevalence of ADHD, aggression, and learning difficulties attributed to attention, memory, and motivation deficits." (4)

MDMA, also known as *ecstasy*, "is a derivative of AMPH that has both stimulant and hallucinogenic properties." (4) It releases serotonin, norepinephrine, and dopamine. (4) Very little is known about the prevalence of MDMA use during pregnancy. However, an increased risk of cardiovascular and musculoskeletal anomalies in MDMA-exposed fetuses has been reported. (4)

PRESCRIBED AND OVER-THE-COUNTER MEDICATIONS

Selective Serotonin Reuptake Inhibitors

The SSRIs (eg, Prozac, Zoloft, Celexa, Lexapro) are a class of antidepressant medications that became available in 1988. (7) In the past few decades, the use of SSRIs has increased due to the increasing incidence of depression. "Women have a strong disposition to depression: 10-20% of women will present with a major depressive disorder during pregnancy and the immediate postpartum period and 5 to 13% of pregnant women will be treated with an SSRI." (43)(44) "Treatment of maternal depression during pregnancy and afterwards at the lowest effective dose is uniformly recommended despite the potential side effects to the fetus and newborn." (7)(44)

The SSRIs have been shown to cross the placenta, and SSRI use, especially during the third trimester, has been shown to increase the risk of an SSRI withdrawal-like syndrome in the newborn that consists of temperature instability, irritability, tremors, poor suck, poor feeding, hypertonia, respiratory distress, seizures, and sleep disturbances, among other symptoms. (7)(44)(45) Neonatal adverse effects are more commonly reported with the prenatal use of paroxetine and fluoxetine and represent the effects of cholinergic and serotonin-induced manifestations of the drug, which regulate cardiovascular, respiratory, and brain functions. (43)(44) These signs occur in 30% of SSRI-exposed neonates and can present within hours to days after delivery and can persist up to 2 to 4 weeks of age consistent with the decline in the serotonin levels of the neonate. (44) Use of SSRIs during late gestation has also been reported to increase the risk of persistent pulmonary hypertension of the newborn (PPHN) by 2- to 6-fold. (44)(45) It is suggested that the persistent pulmonary hypertension of the newborn is secondary to the potent pulmonary vasoconstrictive effects of serotonin. (44) Primary pulmonary hypertension has also been seen in adults with elevated serotonin levels. (44) These adverse effects can increase the risk of NICU admission for the SSRI-exposed neonate. "With respect to teratogenicity, studies vary in quality and design" and present conflicting findings. (45) Most "prospective studies and meta-analyses suggest no increased risk of teratogenicity and SSRI use while studies demonstrating teratogenicity are primarily retrospective and case control in nature, with their inherent limitations." (45)

SEDATIVES (BARBITURATES AND BENZODIAZEPINES)

Barbiturates (ie, phenobarbital) "are classified as sedative/hypnotics because of their CNS depressant and sleep-inducing effects." (46) When prescribed, barbiturates are used as anesthetic and anticonvulsant agents. As with any drug, barbiturate use can be addictive. "The abuse of barbiturates, both licit and illicit, peaked in the early 1970s and declined by the mid 1980s when the treatment of anxiety and insomnia was accomplished with much safer drugs like benzodiazepines." (46) As a result, recent literature is lacking with respect to short- and long-term outcomes of barbiturate-exposed newborns.

Barbiturates freely cross the placenta. (46) "Neonates exposed to barbiturates in utero, especially during the third trimester, can experience an abstinence syndrome similar to NAS." (46) The withdrawal symptoms in barbiturate-exposed babies also tend to begin closer to a week after birth and can last up to 1 month of age. There are some reports of LBW (11) and congenital malformations (ie, neural tube defects, cleft lips and palates, cardiac defects, and microcephaly) in this population of patients. (8)(47) In utero barbiturate use, particularly phenobarbital, may potentially predispose the fetus or newborn to bleeding complications by increasing the rate of oxidative degradation of vitamin K. (48)

Benzodiazepines are commonly prescribed for their sedative effects. Similar to barbiturates, recent literature on the short- and long-term effects of in utero benzodiazepine exposure is sparse. However, it has been shown that benzodiazepines cross the placenta and can accumulate in the fetus. (3) Previous studies have reported signs of benzodiazepine withdrawal in exposed newborns that include hypoventilation, hypertonicity, irritability, and "floppy infant syndrome," particularly after use in late gestation. (3) "These symptoms can appear within a few days to 3 weeks after birth and can last for several months." (3) It has also been previously reported that benzodiazepines increase the risk of preterm birth and LBW. (3) However, there has been no consistent evidence linking this class of drug with congenital anomalies.

TREATMENT OF THE DRUG-EXPOSED NEONATE

Treatment of the drug-exposed neonate often begins with treating the mother. Pregnant women and women of childbearing age should be counseled about the harmful effects of all medications. (12) These women should also be provided support and additional resources to aid them in discontinuing the medication as early as possible. A "public health response" has been initiated by the AAP to promote primary prevention of drug abuse, particularly opioid use, during pregnancy. (14) However, realistically, this is not always possible. For instance, for pregnant women who are already abusing opioids, it is not possible to counsel these women to abruptly discontinue these medications. Instead, they may be prescribed agonist therapy at the most effective dose to stabilize maternal and fetal withdrawal symptoms, reduce cravings for heroin, increase attendance at prenatal care clinics, and promote other positive maternal health behaviors. (4)(9)(14) Since the late 1970s, methadone has been the drug of choice in pregnant women addicted to opioids. Buprenorphine is a more recent alternative to methadone that has been shown to have minimal to mild withdrawal symptoms in the exposed neonate, shorter treatment durations for NAS, and decreased length of hospital stay for the newborn. (6)(7)(25) To date, there has been no consistent evidence to show a relationship between the maternal agonist therapy dose and the severity of NAS. (12)(49)

Maternal opioid maintenance therapies are not without substantial risk as neonatal withdrawal from illicit or prescribed opiates can incite NAS. Nonpharmacologic care is the initial treatment option for NAS. (30) Nonpharmacologic treatment would include providing swaddling, comfort, and a quiet space for the neonate, with minimal overstimulation by light, noise, or handling. (44) If the newborn fails nonpharmacologic measures or the newborn's Finnegan scores reach a threshold level, then pharmacologic treatment would be initiated with 1 of the following regimens: 1) morphine with or without phenobarbital, 2) diluted tincture of opium, 3) methadone with or without clonidine, or 4) the newest option, sublingual buprenorphine. (4)(50) However, tincture of opium is rarely used for NAS therapy due to the need to dilute the medication, thus creating the potential for medication error. (23) "Little empirically based evidence supports the use of one regimen over the other, reflecting a paucity of randomized studies in this area." (3) Evidence suggests that using a standardized protocol for pharmacologic treatment of NAS is more important than the choice of regimen in decreasing treatment days and hospital stays in the exposed newborn. (27)

Most newborns exposed to other substances that can produce withdrawal-like symptoms, such as SSRIs, marijuana, cocaine, nicotine, alcohol, antidepressants, and antipsychotics, do not reach cutoff values for pharmacologic treatment as determined by the Finnegan scoring system. (3) Unlike neonatal opioid withdrawal, generally there are no specific pharmacologic treatments for non–opioid-exposed infants. (3)(37) The non–opioid-exposed neonate is treated based on symptoms, which may require medications or nonpharmacologic treatments. Long-term, all drug-exposed

babies benefit from early intervention services to identify and treat areas of delay in child development. (27)(33)

BREASTFEEDING AND MATERNAL DRUG USE

"Some of the well-known advantages of breastfeeding are the transfer of maternal immunity to the newborn, increase in mother-infant bonding, enhancement of maternal confidence, and active maternal participation in the management of the infant." (30) In the case where a breastfeeding mother is also a substance user, there is some hesitation to encourage breastfeeding because of the possible secretion of these drugs into human milk. "Maternal substance abuse is *not* a categorical contraindication to breastfeeding." (51) However, it is contraindicated if the mother is using illicit drugs such as PCP, cocaine, or marijuana. (51) The AAP recommends that mothers minimize their intake of alcohol when breastfeeding. Their recommendations have been previously published. (51) The AAP also strongly discourages the use of nicotine but states that it is not an absolute contraindication to breastfeeding. (51)

FUTURE DIRECTIONS

Despite the abundance of literature published on the topic of the drug-exposed fetus and neonate, there are still gaps and inconsistencies in knowledge. For instance, "attempts to attribute effects to a specific drug exposure have often been confounded by the use of multiple drugs and limited access to a large diverse population." (38) Long-term outcomes for many drugs of abuse during pregnancy still need investigation beyond the immediate newborn period into childhood, adolescence, and even young adulthood. Optimal strategies for diagnosing drug abuse in utero, for diagnosing withdrawal symptoms, and for treating a symptomatic newborn are still being elucidated. In an era where health care costs are of utmost importance, further research should relate optimal treatment strategies with cost to administer these treatments. In addition, amid the legalization of marijuana in several states and the growing opioid crisis, physicians will have to gain more insight into how to deal with these legal and medical dilemmas to optimize patient care.

CONCLUSION

Maternal substance abuse during pregnancy is an increasing problem in our society that has adverse perinatal and neonatal outcomes. Licit and illicit drug use during pregnancy can have equally detrimental effects on the newborn. Drug-exposed newborns are more likely to be LBW, preterm, and microcephalic; to require delivery room resuscitation and NICU admission; and to have longer hospital stays compared with nonexposed neonates. Primary prevention of maternal drug abuse is optimal, but not always possible. Health care professionals need to become increasingly aware of the signs and symptoms of neonatal drug withdrawal and how to mitigate these symptoms in the newborn period. We should also strive to advocate for these babies beyond the newborn period. Further research and support programs are needed to improve the short- and long-term outcomes and development of the drug-exposed neonate.

Summary

- On the basis of observational studies, babies born to mothers who abuse legal substances such as alcohol and nicotine are at increased risk for low birthweight (LBW), developmental disabilities, and long-term behavioral problems. (3)(4)(6)(9)
- On the basis of observational studies, babies born to mothers who abuse narcotics (ie, opioids) are at increased risk for microcephaly, LBW, admission to the NICU and prolonged hospital stay due to withdrawal symptoms, and long-term cognitive and behavioral impairments. (1)(4)(24)
- On the basis of observational studies, babies born to mothers who abuse illegal substances such as phencyclidine (PCP), marijuana, amphetamines, and cocaine are at increased risk for microcephaly, LBW, abnormal neurobehavioral symptoms, and long-term cognitive delays. (3)(4)(6)(7)(9)(38)
- On the basis of observational studies, babies born to mothers who take prescription or over-the-counter medications such as selective serotonin reuptake inhibitors and sedatives are primarily at risk for persistent pulmonary hypertension of the newborn and withdrawal-like symptoms in the newborn period, respectively. (3)(44)(45)(46)
- On the basis of observational studies, the initial treatment of symptomatic neonates born to mothers who abuse illegal or legal substances involves nonpharmacologic care such as swaddling and comforting the baby. If the baby fails nonpharmacologic therapy, then pharmacologic treatment with medications such as opioids or clonidine may be indicated, especially in opioid-exposed newborns. (4)(30)(44)(50)
- On the basis of observational studies, all babies born to mothers who abuse licit or illicit substances during pregnancy would benefit from long-term developmental follow-up and early intervention services. (27)(33)
- On the basis of expert opinion, breastfeeding mothers who abuse cocaine, marijuana, and hallucinogens (ie, PCP) should abstain from breastfeeding their newborns. (51)

References for this article are at http://pedsinreview.aappublications.org/content/39/11/550.

PIR Quiz

There are two ways to access the journal CME quizzes:
1. Individual CME quizzes are available via a handy blue CME link under the article title in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu or go directly to: http://www.aappublications.org/content/journal-cme.
3. To learn how to claim MOC points, go to: http://www.aappublications.org/content/moc-credit.

1. A newborn boy is admitted to the newborn nursery. He was born to a mother with polysubstance abuse during pregnancy. As you take the pregnancy history, you consider which substances were most likely to have transferred to the fetus by placental drug transfer. Which of the following factors would increase placental drug transfer from the mother to the fetus?
   A. High lipid solubility.
   B. High molecular weight.
   C. High protein binding.
   D. Ionized drug form.
   E. Vasoconstriction.
2. A clinician caring for a group of babies in the special care nursery is notified by the hospital laboratory that a meconium drug screen has returned positive on 1 of the newborns. Meconium drug screening indicates which of the following time frames of drug exposure of this newborn infant before delivery?
   A. Days to 2 weeks before delivery.
   B. In the first trimester of gestation.
   C. Several hours to a few days before delivery.
   D. Several weeks to months preceding delivery.
   E. Within 24 hours before delivery.
3. You are speaking to a group of prospective young primigravida mothers who are early in their pregnancy. The discussion centers around having a healthy pregnancy and delivery. In addition to prenatal care and the importance of prenatal vitamins, you discuss avoiding substances of abuse. Which of the following is the overall most commonly abused substance during pregnancy?
   A. Alcohol.
   B. Cocaine.
   C. Marijuana.
   D. Nicotine.
   E. Opioids.
4. You are caring for a 2-day-old full-term newborn in the well-baby nursery. The baby is manifesting temperature instability, irritability, tremors, poor feeding, and sleep disturbance. Review of the medical records reveals maternal use of selective serotonin reuptake inhibitors (SSRIs) in the third trimester, raising the possibility of these signs as a result of SSRI withdrawal-like syndrome. Which of the following represents the approximate percentage of neonates exposed to SSRIs that will manifest signs of possible SSRI withdrawal?
   A. <5%.
   B. 10%.
   C. 30%.
   D. 60%.
   E. >90%.
5. A newborn baby boy with neonatal abstinence syndrome (NAS) was admitted to the newborn nursery for management. Which of the following is the most appropriate initial treatment option for NAS in this patient?
   A. Diluted tincture of opium.
   B. Methadone with or without clonidine.
   C. Morphine with or without phenobarbital.
   D. Sublingual buprenorphine.
   E. Swaddling, comfort, and minimal overstimulation.

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2018 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2020, however, credit will be recorded in the year in which the learner completes the quiz.

2018 *Pediatrics in Review* now is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics through the AAP MOC Portfolio Program. Complete the first 10 issues or a total of 30 quizzes of journal CME credits, achieve a 60% passing score on each, and start claiming MOC credits as early as October 2018. To learn how to claim MOC points, go to: http://www.aappublications.org/content/moc-credit.

Effect of Maternal Substance Abuse on the Fetus, Neonate, and Child

Nicole A. Bailey and Magaly Diaz-Barbosa

Pediatrics in Review 2018;39;550
DOI: 10.1542/pir.2017-0201

Pediatrics in Review®
AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Effect of Maternal Substance Abuse on the Fetus, Neonate, and Child

Nicole A. Bailey and Magaly Diaz-Barbosa

Pediatrics in Review 2018;39;550
DOI: 10.1542/pir.2017-0201