Journal of Addictive Diseases, 29:175–191, 2010

ISSN: 1055-0887 print / 1545-0848 online
DOI: 10.1080/10550881003684723

Routledge
Taylor & Francis Group

Addiction in Pregnancy

Joan Keegan, DO
Mehdi Parva, MD
Mark Finnegan, MD
Andrew Gerson, MD
Michael Belden, MD

ABSTRACT. Substance abuse in pregnancy has increased over the past three decades in the United States, resulting in approximately 225,000 infants yearly with prenatal exposure to illicit substances. Routine screening and the education of women of child bearing age remain the most important ways to reduce addiction in pregnancy. Legal and illegal substances and their effect on pregnancy discussed in this review include opiates, cocaine, alcohol, tobacco, marijuana, and amphetamines. Most literature regarding opiate abuse is derived from clinical experience with heroin and methadone. Poor obstetric outcomes can be up to six times higher in patients abusing opiates. Neonatal care must be specialized to treat symptoms of withdrawal. Cocaine use in pregnancy can lead to spontaneous abortion, preterm births, placental abruption, and congenital anomalies. Neonatal issues include poor feeding, lethargy, and seizures. Mothers using cocaine require specialized prenatal care and the neonate may require extra supportive care. More than 50% of women in their reproductive years use alcohol. Alcohol is a teratogen and its effects can include spontaneous abortion, growth restriction, birth defects, and mental retardation. Fetal alcohol spectrum disorder can have long-term sequelae for the infant. Tobacco use is high among pregnant women, but this can be a time of great motivation to begin cessation efforts. Long-term effects of prenatal tobacco exposure include spontaneous abortion, ectopic pregnancy, placental insufficiency, low birth weight, fetal growth restriction, preterm delivery, childhood respiratory disease, and behavioral issues. Marijuana use can lead to fetal growth restriction, as well as withdrawal symptoms in the neonate. Lastly, amphetamines can lead to congenital anomalies and other poor obstetric outcomes. Once recognized, a multidisciplinary approach can lead to improved maternal and neonatal outcomes.

KEYWORDS. Addiction, pregnancy, cocaine, alcohol, tobacco, opiates, amphetamines, marijuana, illicit drugs

INTRODUCTION

Illicit drug use during pregnancy is a major risk factor for maternal morbidity and neonatal complications, but despite this fact the prevalence of illicit substance use by women of childbearing age in United States has increased markedly over the past three decades.[1]

Although substance abuse during pregnancy may be increasing, it often remains undiagnosed or under-diagnosed. A recent self-reporting survey by The National Survey on Drug Use and

Joan Keegan, Mehdi Parva, Mark Finnegan, and Andrew Gerson are affiliated with the Lankenau Hospital, Wynnewood, PA. Andrew Gerson and Michael Belden are also affiliated with Thomas Jefferson University, Philadelphia, PA.

Address correspondence to: Joan Keegan, DO, The Lankenau Hospital, Department of Obstetrics and Gynecology, 100 Lancaster Avenue, Wynnewood, PA 19096 (E-mail: keeganj@mlhs.org).

Health from 2002–2003 estimated that 4.3% of pregnant women aged 15 to 44 years reported illicit drug use within the month prior to being questioned.[1,2] Approximately 250,000 women in the United States, of whom 90% are of childbearing age, meet criteria for intravenous drug abuse.[1] This suggests, conservatively, that approximately 225,000 infants born each year could be exposed to illicit drugs in the prenatal or postpartum time period.

Identifying substance misuse in pregnancy can present a significant clinical challenge. In addition, there can be difficulty evaluating the effect of substance abuse on patients' social, behavioral, psychosocial, and biological risk factors associated with both illicit drug use and adverse pregnancy outcomes. Consideration should be given to the implementation of routine antenatal education and counseling of any population identified as having an increased incidence of substance abuse.

The goal of this article is to identify the major categories of drugs and substances that are commonly abused in pregnancy and evaluate the impact these substances may have on the preconception time period, pregnancy, and the postpartum period. Neonatal issues will be addressed elsewhere in this supplement, except in those instances where a pregnancy complication is caused by a specific substance of abuse and affects the newborn directly. Tobacco, caffeine, alcohol, prescription or illicit opiates, and sedative-hypnotics/anxiolytics will be discussed. The most commonly abused illicit drugs of abuse including cocaine, amphetamines, and marijuana will also be addressed. In addition, we will review general guidelines regarding the management of high-risk pregnancies in substance abusing mothers. These guidelines primarily address the identification and management of teratogenic exposure, poor maternal nutrition, intrauterine growth restriction, placental insufficiency, labor management, and maternal/neonatal withdrawal symptoms.

TOBACCO

Preconception

Active and passive tobacco smoking presents major risks to human health. Smoking contributes to the development of various human cancers, respiratory illnesses, and other diseases.[3,4] It is estimated that 21% of American adults smoke. Each year, more than 440,000 Americans die of tobacco-related disease.[5]

Among pregnant women, there is an increased prevalence of smoking among the youngest (<20 years of age) and oldest (>35 years of age) patients. In addition, the lower the level of education achieved, the greater the risk of being a current smoker.[6,7] Studies of tobacco users have shown a 1.2 to 3.6 relative risk for infertility in the preconception period.[8] Every effort should be made to identify smokers prior to pregnancy and provide both psychosocial intervention and pharmacologic methods to enhance the likelihood of smoking cessation. Pregnancy can be a significant motivator to stop or reduce smoking.

Pregnancy

The most recent available statistics on tobacco use in pregnancy report that approximately 12% to 15% of all women continue to smoke during their pregnancy.[9] Tobacco use during pregnancy is associated with a higher rate of pregnancy complications[7] and has a clearly demonstrated dose-response relationship, which can significantly impact both maternal and fetal outcomes. In the first trimester, these risks include an increased risk of spontaneous abortion and ectopic pregnancy. In the second and third trimesters, an increased risk of placental insufficiency, low birth weight, fetal growth restriction, and preterm delivery are all potential morbidities associated with tobacco use. Several studies evaluating the role of smoking during pregnancy report a relative risk ranging from 1.5 to 2.5 for ectopic pregnancy. Spontaneous abortion is 20% to 80% higher in women who smoke in pregnancy compared to non-smokers. Maternal smoking carries a relative risk of 1.2 to 16 for preterm delivery.[8]

Nicotine is one of the 4,000 chemicals that are produced during smoking and at least 43 of these chemicals are known carcinogens.[10] Nicotine has a half life of 1 to 2 hours and is mainly metabolized by the liver and excreted by the kidneys.[8] Nicotine readily crosses the placenta, resulting in a fetal concentration that is

generally 15% higher than maternal and amniotic fluid levels, and 88% higher than maternal plasma levels.[11] Women who smoke are more likely to have a low birth weight baby, with a reported relative risk of 1.3 to 10.[8,12] On average, infants born to women who smoke during pregnancy are 200 to 300 grams lighter. Furthermore, nicotine causes impaired fetal oxygen delivery, resulting in abnormal gas exchange within the placenta and activation of the sympathetic nervous system, increasing the fetal heart rate and causing a reduction in fetal breathing movements.[13]

Carbon monoxide is a major by-product of cigarette smoking that can cause harm to the mother and fetus. Carbon monoxide crosses the placenta and can be detected in the fetal circulation at a level 15% higher than in the maternal circulation.[12] Carbon monoxide diminishes tissue oxygenation via competitive inhibition with oxyhemoglobin, causing decreased availability of oxygen to the fetus.[11] Fanslow et al. concluded that smoking during pregnancy is significantly associated with violence during pregnancy.[14]

Postpartum

Approximately half of women who quit smoking during pregnancy resume smoking within 6 months postpartum and 50% to 90% have relapsed 1 year post-delivery.[12] The likely causes of relapse are stress, lack of sleep, caring for the infant, and concern about weight gain in the postpartum period.[8,12] Smoking during the postpartum period causes a significant health risk for both mother and child. To date, there are no proven effective strategies for preventing relapse during the postpartum period. Close follow-up and positive counseling may be beneficial. Crawford et al. described several strategies for prevention of postpartum relapse. Such strategies include continued counseling, focusing on the health benefits of quitting, and providing reinforcement of the patient's desire to be a good mother.[12]

CAFFEINE

Preconception

Caffeine is a widely available central nervous system (CNS) stimulant and is found in commonly consumed beverages such as coffee, soda, and tea. In addition, caffeine is also used in combination with various drugs, such as aspirin, acetaminophen, codeine, and butalbital. Caffeine has medicinal value because it can be particularly helpful in the treatment of headaches, but it is extremely popular in general use because of its appealing CNS stimulant properties. Caffeine is addictive, and physical dependence is common. Withdrawal from caffeine in adults typically causes jitteriness, a sense of non-well-being, and headaches. Because caffeine is so widely accessible and commonly used by women of childbearing age, its impact on patients in the period of preconception has been widely studied.

Caffeine does cross the placenta, but it does not appear to act as a teratogen when consumed as a component in beverages or over-the-counter medications.[15] The clinical and anecdotal evidence that supports this is relatively vast. However, there has been an ongoing concern regarding the impact of caffeine on fertility. In terms of affecting actual ovulation or causing ovulatory dysfunction, caffeinated beverages appear to be safe and do not impair ovulation.[16] There is a long-standing suspicion, however, that caffeine consumption may be associated with miscarriage or an increased risk of miscarriage. The evidence suggests that this may be the case, and a recent population-based prospective cohort trial showed that consumption of, more than 200 mg/day (about 2 to 3 standard cups of coffee or 4 12-ounce cans of cola) of caffeine may increase the risk of miscarriage.[17] There are no randomized trials to confirm this, and it is unlikely that such a study would be performed.

Pregnancy

During pregnancy, caffeine is probably safe when used in moderation. Again, there is abundant literature and anecdotal experience that suggests there is no obvious association between caffeine use and poor fetal outcomes. However, there may be some association between maternal caffeine use of more than 500 mg/day and fetal cardiac arrhythmias compared to mothers who use less than 250 mg/day.[18]

Postpartum

Caffeine use in the postpartum period will vary from patient to patient, depending on habits and personal preference. Caffeine is excreted in small amounts in breast milk, but in cases of usual moderate consumption the levels are probably too low to be clinically significant. Moderate caffeine consumption is considered to be compatible with breastfeeding.[19]

ALCOHOL

Preconception

Alcohol use is widespread among women of reproductive age. Alcohol is a well-studied teratogen, and its effects on pregnancy can include spontaneous abortion, growth restriction, and birth defects. The incidence of alcohol use in non-pregnant women ages 15 to 44 years is 53%. It is estimated that as many as 24% of young women who drink are binge drinking.[20] Oftentimes, conception occurs during times of alcohol use or abuse and women continue casual drinking into the first trimester until they are aware of their pregnancy. The development of all fetal organ systems can be affected at this early stage during the first trimester. Therefore, the preconception period is an important time to identify women at risk.[20]

In the preconception period, each encounter with patients can be an opportunity to screen for alcohol use or abuse and intervene to reduce or completely stop alcohol consumption. There are several screening tools available. Questions to ask are detailed in mnemonics such as Take, annoyed, cut down, eye opener (T-ACE), Tolerance, Worried, Eye-opener, Amnesia, and K/Cut down (TWEAK), or Alcohol Use Disorder Identification Test (AUDIT).[21] The United States Preventative Services Task Force, the American College of Obstetrics and Gynecology, and the American Academy of Pediatrics suggest using preconception and prenatal visits to discuss the benefits of abstaining from alcohol. There are no evidence-based studies to suggest any amount of alcohol use is safe during pregnancy.

Pregnancy

During pregnancy, the fetus that is exposed to alcohol can be severely affected. Fetal alcohol spectrum disorder (FASD) encompasses a wide range of disorders defined as prenatal and postnatal growth restriction, central nervous system abnormalities, and craniofacial abnormalities. Some common fetal conditions associated with alcohol abuse include facial dysmorphogenesis, cardiac septal defects, and joint abnormalities. Infrequently, other anatomic or physiologic abnormalities are found. These include abnormalities of the eyes, hearing issues, urinary problems, immune system deficiencies, and skeletal problems. FASD is permanent and has a significant affect on the baby and family. Centers for Disease Control and Prevention (CDC) studies show FASD rates ranging from 0.2 to 1.5 per 1,000 live births in different areas of the United States.

Alcohol abuse and misuse in pregnancy is the most common non-genetic cause of mental retardation.[22] There is strong medical evidence to suggest that heavy alcohol use or binge drinking can lead to high rates of fetal alcohol spectrum disorder.[22] Studies show that even small amounts of alcohol used on a daily basis can be detrimental to the fetus.[22]

Postpartum

Little data exist regarding the postpartum period and alcohol use. This time can be stressful for any mother, and particularly so if the mother is alcohol dependent. As we become more aware of the importance of identifying women at risk for postpartum depression, it may be prudent to include those mothers who are identified as using alcohol during their pregnancy as a potential focus. The postpartum visit may be a good time to screen women for alcohol abuse. The Healthy Moms Trial supports the implementation of brief alcohol intervention during the postpartum period.[23]

OPIOIDS

Preconception

The class of drug known as the opioids contains the opiates, which are natural or

semi-synthetic morphine-like substances, as well as the fully synthetic opioids. Opiates include morphine, codeine, and heroin. Meperidine, fentanyl, propoxyphene, and methadone are synthetic opioids.[20] Most of the information available regarding the effects of opioids on pregnancy is derived from studies of patients who have used heroin or methadone. There has been a recent increase in the use of prescription opioid analgesics, such hydromorphone and oxycodone, during pregnancy.

The prevalence of opiate use in pregnant women ranges from 1% to 21%.[6] The higher number reflects use in at-risk populations and does not represent overall use in a more standard obstetric population. Heroin is the most commonly abused illicit opiate and crosses the placenta readily. Heroin enters the fetal tissues within 1 hour of maternal use.[19] Women who use heroin are likely to use other harmful substances, such as tobacco, alcohol, and cocaine, all of which have their own potential adverse effects on pregnancy. Therefore, it is difficult to separate the effects of heroin from these other substances. Heroin can be mixed with other substances, including amphetamines, which can have independent detrimental effects on the pregnancy and fetus. In addition, intravenous drug use is a risk factor for many infectious diseasesm, including cellulitis, endocarditis, chorioamnionitis, and human immunodeficiency virus (HIV) infection, which can further complicate pregnancy.

Pregnancy

Pregnant women who use heroin can experience a six-fold increase in maternal obstetric complications,[24] includig intrauterine growth restriction, third trimester vaginal bleeding, malpresentation, preterm delivery, and puerperal morbidity. In addition, stillbirth, decreased infant head circumference, depressed Apgar score, meconium staining of the fetus, and chorioamnionits are all increased in heroin users.[22] Neonatal abstinence syndrome is seen in 50% to 95% of infants exposed to heroin.[22] Neonatal withdrawal is well described and is the most common finding in opiate-exposed neonates is CNS irritability. Supportive care is most important for these babies.[19]

Prenatal and antepartum care for patients using heroin must be tailored to these patients' special needs. Testing for sexually transmitted infections, such as HIV, syphilis, gonorrhea, chlamydia trachomatis, and hepatitis B and C, should be included in routine care and repeated periodically throughout the pregnancy. The provider must counsel the patient regarding the effects of heroin on herself and the fetus. In addition, the physician needs to counsel the patient on the potential benefits of methadone maintenance instead of continued heroin use. Methadone is a synthetic opioid that can be taken orally, and this treatment strategy has multiple benefits. Methadone is inexpensive and can dramatically reduce the incidence of criminal behavior. It may diminish exposure to needleborn infections, including HIV and hepatitis. Typically, patients using methadone can more easily make the transition to a life that is free of heroin abuse. Methadone maintenance clinics should be made available to help patients addicted to heroin, and the obstetrician should collaborate with the clinic to facilitate comprehensive care. Each prenatal visit should be used to evaluate the patient for signs of opiate toxicity and withdrawal. Symptoms of intoxication include drowsiness, decreased respirations, miosis, constipation, and diminished drug seeking. Withdrawal signs include drug craving, lacrimation, sweating, anorexia, diarrhea and flushing.[22]

Methadone maintenance treatment of pregnant women using heroin can be beneficial, as suggested above. In a 1995 position paper, United States federal guidelines regarding the regulation of methadone recommended preferential admittance to pregnant women with heroin addiction into methadone treatment programs.[25] Women taking methadone demonstrate reduced use of illicit drugs, better compliance with prenatal care, and improved newborn birth weight.[24] In most circumstances, withdrawal from methadone is rarely appropriate during pregnancy,[25] but occasionally there may be instances when withdrawal may be helpful. Aggressive attempts at withdrawal can lead to withdrawal symptoms in the mother and fetal withdrawal and possibly intrauterine fetal death.[19] It is crucial for the obstetrician to

identify patients using heroin and help them initiate a treatment program.

Opioid analgesics such as oxycodone and hydromorphone can be judiciously used in pregnancy with close supervision but are much more commonly used in the post-partum time period for post-delivery pain control following both vaginal deliveries and cesarean sections. No congenital anomalies have been reported in babies born to patients who use hydromorphone for prolonged periods. Oxycodone use in pregnancy has also not been associated with any major birth defects.[19] However, the use of both substances increases the risk of neonatal withdrawal, particularly if they are used in and around the time of delivery.

Postpartum

Patients frequently use opioid analgesics in the postpartum period. Opioids are excreted into breast milk in small quantities. Minimal, if any, effect on the newborn is clinically significant. However, the neonate should be observed for signs of adverse effects, such as gastrointestinal side effects, sedation, and feeding pattern changes. For heavy narcotic abusers and women in methadone treatment programs, the postpartum time period is an excellent time to readdress the possibility of gradual narcotic withdrawal and continued rehabilitation.

SEDATIVE-HYPNOTICS AND ANXIOLYTICS

Preconception

The classes of drugs commonly known as the barbiturates and benzodiazepines fall into the larger category of drugs called the sedative-hypnotics and anxiolytics. Barbital, first introduced in 1903, is a derivative of bartituric acid and had noteworthy sleep-inducing and anxiolytic effects tat made it instantly popular from a clinical standpoint. Other barbiturates, such as phenobarbital, have anti-convulsant properties which also make them clinically useful. These anti-convulsant barbiturates are not commonly associated with abuse or addiction. As pharmacology progressed, the separation of the anti-convulsant properties from the sedative properties of these medications led to the development of the benzodiazepines, which are widely available as prescription treatment for anxiety and insomnia, and have a high propensity for abuse.

Currently, there are only a few barbiturates remaining on the market, and they remain in use because of their depressive CNS properties, particularly in the treatment of headache. Specifically, butalbital, the active agent in fiorocet and fiorinal, remains in common use for the treatment of migraines. Migraines are more common in women, especially those of reproductive age women. Therefore, several patients will conceive while using fiorocet or fiorinal and may require these drugs for control of their migraines in pregnancy.

Fiorocet and fiorinal are both Food and Drug Administration Fetal Risk Summary category C drugs,[26] suggesting that there are no controlled studies of their teratogenic effects on the human fetus, and that these drugs should only be used if the benefits outweigh the risks. For most patients who suffer with migraines, the benefits do indeed outweigh the theoretical risks inherent in the use of barbiturate-containing medication. The literature that evaluated the safety of barbiturate use in pregnancy is somewhat dated; the work was done primarily in the 1970s and 1980s. A review of this literature suggests that no increased risk of fetal malformation was noted above expected levels of occurrence, but that severe neonatal withdrawal is a critical consideration, particularly if the mother is a heavy butalbital user close to the time of delivery.[19]

Benzodiazepine use in the preconception time period is not uncommon because of the appeal of these medicines, particularly for the treatment of anxiety. Benzodiazepines are generally category D drugs, reflecting positive evidence of fetal risk. This risk must be weighed against the seriousness of the condition for which the mother is being treated. The risk of benzodiazepine abuse is relatively high, and fetal exposure has been extensively studied. There is conflicting evidence regarding the teratogenicity of benzodiazepines, with the suggestion of an increased likelihood of multiple anomalies, including cleft lip and palate, fetal growth restriction, and intrauterine fetal death. Still, no study or meta-analysis

has been able to definitively link benzodiazepine abuse with a specific neonatal syndrome or constellation of anomalies, so the overall risk to the fetus in the face of exposure may in fact be low.

Pregnancy

Barbiturate abuse is relatively uncommon, but the powerful sedative effects that initially made these drugs attractive continue to have some appeal. There are patients who, secondary to severe migraine or headache pain or because of addiction, continue to be heavy users during pregnancy. As suggested above, there appears to be no significant teratogenic effects associated with barbiturate abuse.

Benzodiazepine use in pregnancy should raise physician awareness of the potential abuse of other substances, including alcohol and tobacco. As mentioned, the risk to the exposed fetus may be minimal, but the abrupt cessation of benzodiazepine use by the mother should be avoided because of the severe withdrawal symptoms associated with rapid cessation, including suicidal ideation.

For patients who are noted to be heavy users of sedative-hypnotics in pregnancy, a rehabilitation program could be considered. In addition, an evaluation by a psychiatrist or headache/migraine specialist may help the patient make the transition away from addictive medications. It should be emphasized to the patient that there can be significant withdrawal symptoms observed in the newborns of barbiturate or benzodiazepine addicted mothers, and these babies should be identified to the neonatology team.

Postpartum

The postpartum time period can be emotionally exhausting, even for the healthiest, non-addicted mother. For patients who have known drug dependency, the postpartum period can be particularly challenging. There are also several patients who suffer with anxiety or headache/migraines and notice an exacerbation of these conditions during the post-delivery period. For sedative-hypnotic abusers, careful attention must be paid to the amount of drug used, and whether the patient is breastfeeding. Sedative-hypnotics are generally contraindicated or considered possibly unsafe in lactation because of the sedative properties of these medications are readily excreted in breast milk.

COCAINE

Preconception

According to a 2005 government survey, approximately 4% of women use illicit drugs during their pregnancy, and cocaine is one of the most commonly abused drugs.[27] Prenatal cocaine use is commonly associated with poor pregnancy and adverse birth outcomes, and cocaine abuse particularly impacts measures of fetal growth and well-being. Low birth weight, intrauterine growth restriction, and decreased head circumference are all noted to be increased in newborns of mothers who use cocaine in pregnancy. In addition, cocaine use is frequently associated with inadequate prenatal care and the frequent concomitant use of tobacco and alcohol.[28] Moreover, cocaine use is associated with psychosocial, behavioral, and biomedical risk factors, such as poverty, poor nutrition, stress, depression, physical abuse, lack of social support, and sexually transmitted infections,[28] all of which can greatly affect pregnancy outcome.[29]

Pregnancy

Maternal cocaine use may have both direct and indirect effects on the fetus. Cocaine rapidly crosses the placenta and a higher concentration occurs in the fetus. There are many adverse outcomes associated with cocaine use during pregnancy. Cocaine use during the early months of pregnancy can cause spontaneous abortion. Up to 38% of early pregnancies may result in miscarriage in cocaine-abusing mothers.[28] This increase in incidence of spontaneous abortion is probably secondary to an increase in maternal plasma norepinephrine, which increases uterine contractility, constricts placental vessels, and decreases blood flow to the fetus. Placental abruption accounts for 2% to 15% of adverse effects of cocaine use during pregnancy. Abruption is

thought to be caused by vasospasm and hypoxia of the placental bed, and it is more common with cocaine binging than with regular use. As a result of maternal cocaine use and placental abruption, the incidence of stillbirth in cocaine-abusing mothers is elevated 8% above the expected level when compared to the general population.[28,30]

Cocaine stimulates uterine contractility through β-agonist action on the β_2-receptors of the uterus. The consequence of this β-agonist property is an increased risk of premature preterm rupture of membranes, preterm labor, and preterm delivery. These adverse outcomes are observed in 17% to 29% of pregnancies of cocaine-abusing mothers. Intrauterine growth restriction (IUGR) and low birth weight can be observed in 22% to 34% of all infants exposed to cocaine in utero, secondary to the constriction of the uterine blood vessels, which leads to intermittent hypoperfusion of the uterus and placenta.[31] Moreover, cocaine significantly suppresses maternal appetite which contributes to poor maternal and fetal nutrition.[30,31]

Cocaine exposure can affect embryonic and fetal development. Congenital anomalies have been reported to occur in 7% to 40% of infants exposed to cocaine in utero. Evidence of brain malformation and cardiovascular abnormalities can occur in approximately 35% and 4% to 40% of exposed fetuses, respectively.[32]

Postpartum

The mainstay of the management of the cocaine-addicted mother and newborn immediately following delivery is supportive care.[30] Although the symptoms of cocaine neurotoxicity are not often life threatening for the mother or the newborn, these symptoms are extremely unpleasant.[30–33] For the mother during the postpartum period, mood symptoms and, less commonly, hallucinations may require treatment with antipsychotic medications, particularly during the inpatient stay.

From a social-focused and family-focused standpoint, the use of cocaine is extremely problematic. Cocaine use during pregnancy is considered a significant risk factor for infant neglect and abuse. Evidence of cocaine use in pregnancy often results in the removal of the infant from maternal custody within the first 18 months of life.[34] Prospective studies have also indicated a strong link between cocaine-using mothers and child maltreatment, with high rates of care-giving disruption (43%) and child maltreatment by 2 years (9% to 23%).[34] Finally, a stable and secure home environment helps reduce the stressors associated with cocaine addiction, so any intervention in this regard may be extremely helpful.

AMPHETAMINES

Preconception

Amphetamines are powerful CNS stimulants with a profound ability to increase wakefulness and focus. The principle mechanism of action is increased release of norepinephrine, serotonin, and dopamine from neurons within the brain. At the same time, amphetamines inhibit re-uptake of these neurotransmitters. Amphetamines are commonly used as drugs of abuse, particularly methamphetamine (also known as "crystal-meth"). Drugs in the amphetamine family can also serve traditional medicinal purposes. Amphetamine/dextroamphetamine (Adderal) is an effective treatment for attention deficit hyperactivity disorder and is used frequently by women of reproductive age. Fortunately, this is not a commonly abused medication in pregnancy.

Information about amphetamine use in pregnancy and preconception is less than reliable due to the fact that the studies are retrospective or depend on voluntary maternal reporting. However, amphetamine use, particularly among young pregnant patients, appears to be increasing.[35] The effects of amphetamine use in the preconception period and pregnancy are difficult to establish because users of amphetamines will commonly use other illicit drugs while pregnant, making it difficult to separate the effects of amphetamines from those of other illicit drugs. As with virtually all other drugs of abuse, there is an important confounding effect. More important, perhaps, is the association of amphetamine use with risky sexual behaviors, teenage pregnancy, and potential increased risk of sexually transmitted infections.[36]

Pregnancy

In animal studies, cleft palate, exencephaly, growth insufficiency, retinal defects, and delayed motor development have been reported as being associated with amphetamine use during gestation.[37] There are case reports suggesting an association of increased congenital abnormalities in human fetuses exposed to amphetamines during the first trimester. These defects include heart defects, gastroschisis, small intestinal atresia, and cleft lip and palate.[38–42] Other studies have not shown any association with increased risk of fetal malformation.[43–45] Overall, amphetamine abuse does not seem to be associated with any consistent increase in congenital abnormalities above the background 3% population risk. Furthermore, there is no evidence of a consistent syndrome associated first trimester amphetamine use. Thus, current thought is that amphetamines are not human teratogens.[19,46]

Fetal growth insufficiency has been reported to be associated with amphetamine use in pregnancy. It is unclear if this is related to a direct effect of the agent on the placenta or fetus or whether this represents a nutritional problem in patients who use amphetamines.[37,44,46–48] There are also reports of fetal/neonatal cerebral cavitary lesions in patients who use amphetamines during pregnancy. It is hypothesized that this may be due to hypoxic injury related to amphetamine-induced vasoconstriction.[19]

Patients who are known to use amphetamines should be encouraged to stop, and there seems to be no detrimental effect associated with discontinuation of use during pregnancy. The patient should be referred to a substance abuse program. In addition to routine obstetric care, management of patients who are users of amphetamines should include frequent ultrasounds to assess the growth and integrity of the central nervous system of the fetus. The neonatologist needs to be alerted regarding possible maternal abuse of amphetamines at the time of birth so neonatal symptoms can be recognized and treated, if warranted.

Postpartum

Information addressing amphetamine use in the postpartum period is scant, but amphetamine use during lactation is considered possibly hazardous. Mild neonatal withdrawal has been described, including jitteriness, drowsiness, and respiratory distress.[19,49,50] Maternal methamphetamine use may have long-term detrimental effects on exposed fetuses, and exposure may result in future learning and memory impairments.[51]

MARIJUANA

Preconception

Marijuana has been reported to be used by 3% to 16% of all pregnant patients.[19,52,53] Like all substances of abuse in pregnancy, there are no prospective studies establishing the actual rate of marijuana use and the statistics cited depend on voluntary patient reporting. The effects of marijuana use on a developing fetus in the preconception time period and pregnancy are hard to establish because users of marijuana will frequently use other illicit drugs while pregnant, making it difficult to separate marijuana's effects from the effects of other drugs. Again, self-reporting is a confounder.

Delta-9-tetrahydrocannabinol is the active ingredient in marijuana and it readily crosses the placenta. However, marijuana is not a pure substance. Commonly available marijuana varies in potency and may have up to 400 other chemicals and substances admixed. Separating out the effects of these chemicals, as well as the effects of varying potency, is a confounder in any report or statistics that address marijuana use in pregnancy. There is no known increase in the risk of congenital abnormalities above the background risk of 3% in patients who smoke marijuana in the first trimester.

Pregnancy

There is no known increase in pregnancy complications for users of marijuana.[19] There has been a suspicion that patients who use marijuana during pregnancy may have longer gestations.[19] However, other studies have suggested a shorter gestation.[54] Thus, the data concerning the effect of marijuana on gestational length is contradictory. There has been some suggestion of longer,

dysfunctional labors in patients who smoke marijuana around the time of delivery, but other reports fail to confirm this.[19] There is also a suggestion that there may be an association between marijuana use and an increase in low birth weight and small for gestational age infants.[55] However, other reports do not confirm this.[55–58]

Patients who are known to use marijuana during pregnancy should be counseled about the associated risks and encouraged to stop. Intervention programs should be offered. In addition to routine obstetric care, patients who use marijuana during pregnancy should have follow-up ultrasounds at 28 and 36 weeks to confirm adequacy of fetal growth. At the time of delivery, the pediatric team should be alerted regarding maternal marijuana use during pregnancy.

Postpartum

Marijuana use in the postpartum time period has not been well studied. There is limited clinical evidence to drive recommendations regarding counseling, intervention, or rehabilitation. Therefore, care for the marijuana-addicted mother must be approached on a case-by-case basis, and social work consultations should be used liberally in an attempt to stabilize the home environment as much as possible. As mentioned above, marijuana is frequently used in conjunction with other drugs and substances of abuse.

MANAGEMENT OF HIGH-RISK PREGNANCIES IN SUBSTANCE ABUSING MOTHERS

General Considerations

The substance-abusing mother by definition is considered high-risk, with significant exposure for maternal and fetal complications. In the prior discussions of the various different substances of abuse, these risks are identified individually, with particular attention paid to the most likely maternal and obstetric complications. As a general rule, teratogenicity, poor maternal nutrition, IUGR, poor placental perfusion and function (placental insufficiency), labor management, and withdrawal syndromes are the most common obstetric issues that must be addressed when considering the impact of substance abuse on pregnancy. In the case of cocaine abuse, placental abruption and stillbirth are important additional considerations.

Teratogenic Exposure

The possibility of substances of abuse causing fetal anomalies is an overriding concern, and specific considerations are mentioned for the drugs and substances of abuse discussed. Alcohol abuse in particular is highly associated with FASD, which can be manifested as structural anomalies or developmental defects, including fetal growth restriction. Mental retardation, developmental delay, and behavioral disorders are common components of FASD and can also be seen in the children of cocaine abusing mothers. Cocaine is also associated with fetal brain and cardiac malformations, and amphetamine use is associated with cavitary brain lesions. In regard to management of these problems for the expectant mother, little can be offered once the damage has been done. No prenatal test is currently available to help identify fetuses at risk for future mental retardation and developmental delay. From an obstetric standpoint, only early ultrasound identification of structural anomalies is a possibility. Once an anomaly has been identified, various pediatric specialists can be consulted for post-delivery management if this is appropriate. Serial ultrasonographic surveillance of the fetus, with the addition of frequent non-stress testing, contraction stress testing, or biophysical profiles, may have some additional value (these tests and surveillance strategies will be addressed below).

Because none of the substances of abuse discussed earlier are associated with fetal aneuploidy or chromosomal anomalies, amniocentesis or chorionic villus sampling for genetic testing should be performed only as indicated or desired by the parents—it yields no further information in regard to predicting the possibility of future retardation or developmental delay. In instances where significant fetal anatomic anomalies are observed with routine sonographic screening, it is reasonable to offer pregnancy termination to the patient, particularly if the anomaly noted would be incompatible with

life. These instances must be approached in a case-by-case basis.

Nutritional Considerations

Poor maternal nutritional status is associated with many substances of abuse. Smoking, alcoholism, opiate abuse, sedative/hypnotic abuse, cocaine abuse, marijuana abuse, and amphetamine abuse have all been associated with poor maternal weight gain and nutritional status. In many cases, these substances are mixed, and most have fairly powerful appetite suppressant properties. Management of poor maternal nutrition is relatively concrete in theory but can be frustrating for the practitioner because sometimes little can be done to change established maternal behaviors in regard to nutrition. A multi-disciplinary approach incorporating nutritional counseling by trained dieticians or nutrition counselors can certainly be valuable. Frequent weight checks and fetal surveillance for IUGR should be incorporated into routine obstetric care for substance abusing mothers.

Ideally, substance abusing mothers should be counseled extensively regarding the importance of balanced nutrition, including recommendations regarding caloric intake and appropriate weight gain. Body mass index should be calculated as well because there will certainly be a significant number of substance-abusing pregnant patients who may be obese or severely underweight; both of these conditions suggest poor overall nutritional status. Nutrition counseling should focus on a well-balanced diet and the inclusion of nutritional foods. Exercise can be emphasized at these counseling sessions as well.

Dietary allowances of most vitamins and minerals increase during pregnancy, and prenatal vitamins can play an important role in supplementation. In particular, iron supplementation (27 mg of additional daily iron) should be included in the daily diet. Iron deficiency anemia is a common problem in the substance abusing population, and an additional 60 to 120 mg of iron is recommended for these individuals. Vitamin C facilitates the absorption of iron, and additional vitamin C may need to be added. Folic acid supplementation should also be addressed, particularly in the preconception period and first trimester because of the known association between folic acid supplementation and a diminution in risk of spina bifida. Caloric intake is generally calculated at 25 to 35 kcal/day of optimal body weight. An additional 100 to 300 kcal/day is recommended in pregnancy.[59]

Intrauterine Growth Restriction and Placental Insufficiency

Because of the high correlation between substance abuse and poor maternal nutrition, as well as the impact of substances of abuse on placental function, surveillance for appropriate fetal growth and placental function is an important component of care for substance-abusing mothers. Again, like many recommendations that are made to substance abusers, compliance can be an issue. Nevertheless, obstetricians should be vigilant in their attempts to follow substance-abusing mothers as closely as possible in the antenatal period, particularly in the attempt to identify suboptimal fetal growth and placental insufficiency. In many instances, IUGR and poor placental function increase the risk of stillbirth, and it is for this reason that vigilance is urged. Alcohol abuse, smoking, and illicit drug use are all strongly associated with IUGR and stillbirth, although it can be extremely difficult to differentiate the actual effect of the drug or substance of abuse on the fetus from other maternal behaviors which are associated with drug use.[59]

Recommendations regarding surveillance for fetal growth and placental function generally involve serial uterine fundal height measurements and serial ultrasound evaluation of the fetus with attention paid to fetal head circumference and biparietal diameter, abdominal circumference, amniotic fluid indices, and Doppler velocimetry. Serial ultrasound surveillance typically begins at approximately 20 weeks of gestation and continues at 4-week intervals thereafter. Non-stress testing, contraction stress testing, and the biophysical profile can be used as well, depending on the clinical situation; these tests are typically performed in the third trimester. Uterine fundal height measures can be an effective screening tool for IUGR and should be performed at every prenatal visit after 20 weeks of gestation. When

a patient has a smaller than expected fundal measurement, the suspicion of IUGR should be confirmed with directed ultrasound in a timely manner. Specifically, ultrasound measures of the biparietal diameter (distance across the fetal head), head circumference, abdominal circumference, and femur length should be measured to obtain the most accurate estimated fetal weight. The amniotic fluid index should also be measured. Pockets of amniotic fluid are measured in all four quadrants of the uterus and a cumulative measure of the vertical pockets should be greater than 5 cm. A measure less than 5 cm would suggest oligohydramnios (low amniotic fluid), and this can be cause for concern because it may indicate a long-term diminution in placental function. In fact, oligohydramnios or anhydramnios (no measurable amniotic fluid pockets) may indicate a need for delivery, depending on the clinical circumstances. In general, ultrasound evaluation should occur every 2 to 4 weeks if IUGR is suspected. An interval less than 2 weeks can introduce the possibility of measurement errors.

Fetal non-stress testing or contraction stress testing may also be of value in the ongoing surveillance of substance abusing mothers, particularly if IUGR, placental insufficiency, or oligohydramnios is suspected or diagnosed. Non-stress testing can be performed on an outpatient or inpatient basis and assesses utero-placental function by evaluating the fetal heart rate over a 20-minute period of time with an external fetal heart rate monitor. The presence of accelerations of the fetal heart rate is associated with fetal movement and appropriate placental perfusion and function, and is considered reassuring. A non-stress test is reactive if there are 2 accelerations of at least 15 beats per minute above the established baseline lasting at least 15 seconds in a fetus greater than 32 weeks or 10 beats per minute above baseline lasting at least 10 seconds in a fetus less than 32 weeks within a 20-minute period. The contraction stress testing assesses utero-placental function by measuring the fetal response to induced or spontaneous contractions. A positive contraction stress testing occurs when late decelerations (an observed slowing of the fetal heart rate) occur with more than half of the contractions in a 10-minute time period. Contraction stress testing is a more cumbersome test to perform, however, and is used less commonly than the non-stress test.

The biophysical profile assesses fetal well-being using 5 biophysical components, including 4 findings determined by ultrasound in combination with a fetal heart rate non-stress test. The biophysical profile can be a useful test by itself and can also be used as an adjunct or confirmatory test if fetal non-well-being is suspected. Normal measurements are scored as 2 points and abnormal measurements are scored as 0 points. The following parameters (all observed with ultrasound) are also assigned 2 points: fetal breathing, fetal movement, fetal tone, and the amniotic fluid index. Thirty minutes of total ultrasound observation is allowed.

When IUGR is suspected and confirmed in a substance-abusing mother, the possibility of perinatal death or stillbirth becomes an important consideration. IUGR can almost never be reversed, but careful surveillance, particularly with Doppler velocimetry of the umbilical artery waveform, is associated with a reduction in perinatal death.[59] Umbilical artery Doppler velocimetry assesses umbilical artery blood flow by measuring vascular impedance. The systolic to diastolic ratio is abnormal when it is greater than the 95^{th} percentile for gestational age or if diastolic flow is either absent or reversed.

Timing of delivery can also be a challenge in the growth-restricted fetus. The practitioner must weigh the risks of prematurity versus the ongoing risk of intrauterine fetal death if poor fetal growth or placental insufficiency is suspected. In general, absent or reversed end-diastolic flow observed with Doppler velocimetry can be an indication for delivery. Other indications for delivery included oligohydramnios and anhydramnios. Complete absence of fetal growth observed in consecutive ultrasound evaluations 2 to 4 weeks apart may also provide a strong indication for delivery. Mode of delivery (cesarean section versus vaginal delivery) should be individualized based on the patient and her obstetric considerations. For patients with a vertex fetus and reassuring fetal surveillance testing, an induction of labor with planned vaginal delivery is acceptable. A planned cesarean section may be indicated in circumstances when fetal surveillance testing is non-reassuring, the fetus

is breech, or there is a low likelihood that the fetus would be able to tolerate labor.

Labor Management

Management of the substance-abusing patient in labor can present significant challenges to the obstetrical team. As a general rule, the labor and management of the substance-abusing patient should be based on widely accepted obstetric practice and recommendations, which are beyond the scope of this article. There are two issues, however, that merit special consideration—communication with the patient and management of anesthesia.

Establishing healthy and non-threatening communication with a substance-abusing mother in labor is a paramount goal for obstetrical caregivers. Nurses, physicians, and midwives must work diligently to put the patient at ease and inform her that there is a potential for many necessary obstetric interventions, all of which will be done to maximize the likelihood of a good outcome for the mother and her baby. Unfortunately, establishing lines of communication can be frustrating, particularly when addicted patients present exhibiting erratic, bizarre, angry, or uncaring behavior.[60]

Inhaled cocaine users will frequently obtain this drug when labor begins because of a fear that labor anesthesia and analgesia will not be offered or will be inadequate on presentation to the hospital. This behavior has been exhibited in narcotic abusers as well. The addicted mother can cause increased stress for the obstetrical staff, and establishing a trusting relationship with the patient by speaking in a calm voice, utilizing appropriate physical contact, and using soft lighting can all be beneficial as the caregiver attempts to gain control of a potentially chaotic situation. It must be emphasized to the patient that all indicated interventions are for her benefit. Finally, using appropriate referrals, particularly to case managers, social workers, and home nursing services, can be beneficial in helping to organize the post-delivery care for substance-abusing mothers. These referrals also provide the opportunity to keep ongoing communication with the patient intact.[60]

Considerations regarding labor anesthesia and analgesia are particularly relevant when a substance-abusing patient presents in labor. Each particular substance of abuse brings its own challenges. Tobacco use affects the pulmonary system and increases sputum and secretion production, as well as impairment of gas exchange. Cigarette smoking may also affect hepatic enzyme function and may alter metabolism of the induction agents used for general anesthesia. Therefore, regional anesthesia is preferred and can help caregivers avoid the potential problems associated with bronchospasm and airway manipulation.[61]

Alcohol-abusing patients present significant challenges when they present in labor. A blood alcohol level of 25 mg/dL is associated with significant impairment, and intoxication is typically defined as a blood alcohol level greater than 100 mg/dL. Alcohol intoxication increases gastric acidity and diminishes the ability to protect the airway. Chronic liver disease, coagulopathies, pancreatitis, and esophageal varicies must be considered based on the clinical presentation of the patient, and appropriate blood testing is indicated at the time of presentation, particularly for the evaluation of a potential coagulopathy. Regional anesthesia is usually the optimal choice for alcohol-abusing patients and is safe if the patient does not suffer with an underlying neuropathy or clotting disorder. Intravascular volume must be optimized before the administration of regional anesthesia, especially in the face of clinical dehydration. Optimal fluid resuscitation will diminish the potential adverse effects of sympathetic blockade. Alcohol withdrawal syndrome, which is common, should be managed with benzodiazepines, alpha-2 agonists, or the resumption of alcohol consumption.[61]

Opioid abuse in the laboring patient presents several problems, including respiratory depression and arrest. Regional anesthesia/analgesia is widely considered to be safe in opioid abusers. Patients who present with recent opioid use may have diminished anesthetic requirements. Conversely, chronic use may increase tolerance and chronic abusers may require higher anesthetic and analgesic doses than would be anticipated. Mothers using methadone maintenance regimens should be treated as usual; the key point

is that their methadone should not be withheld unless there is a strong clinical indication to do so. There is no reason to believe that methadone maintenance patients will have lower pain requirements than other patients.[62]

Cocaine abuse in pregnancy can present life-threatening complications to both the mother and fetus, including acute myocardial infarction and placental abruption. Therefore, the cocaine-abusing mother must be given particular consideration. Hypertension, tachycardia, arrhythmias, seizures, fever, and emotional instability are all associated with cocaine abuse. Regional and general anesthesia can both be complicated in cocaine users. Cocaine-induced thrombocytopenia can present a contraindication to regional anesthesia or analgesia. Epidural or spinal placement can be further jeopardized by the agitated patient and intrathecal opioids administered in labor typically have a shorter duration in cocaine-abusing patients.[62]

General anesthesia administered to the cocaine-abusing mother presents additional challenges. Halothane should be avoided because it sensitizes the myocardium to the effects of catecholamines. Cardiac arrhythmias and increased systemic vascular resistance have been associated with the use of isoflurane. Currently, there is no information available regarding the use of sevoflurane or desflurane. Propofol, which is commonly used in the United States, is safe and effective for the induction of anesthesia in cocaine-abusing mothers.[62]

The management of hypertension in cocaine abusers can also be challenging. Beta-blockers can cause unopposed alpha stimulation and associated vasoconstriction of the coronary arteries. Labetolol, a combined alpha and beta blocker, is widely considered to be safe and does not impede uterine blood flow. Hydralazine may cause a significant maternal reflex tachycardia.[62]

Amphetamines affect the serotonin and dopamine systems, as described previously. The profound CNS findings commonly seen in amphetamine users, including increased alertness, decreased fatigue, and euphoria, can make placement of regional anesthesia difficult. Maternal hypertension, tachycardia, and arrhythmias all mimic the side-effects associated with cocaine abuse and should be treated accordingly. Inhalation agents should be used with caution, as is similar with cocaine-abusing patients.[62]

Patients presenting in labor with recent marijuana use often experience myocardial depression and tachycardia, which should be taken into consideration when anesthesia and analgesia are administered. Marijuana may also potentiate the sedative-hypnotic effects of other anesthetic agents and may cause increased tolerance of medications, including benzodiazepines and opioids, which may need to be given for medical indications. Heavy marijuana use may impair lung function, and drugs that may be likely to cause tachycardia should be avoided.[63]

Management of Withdrawal Symptoms

Issues arising as a result of maternal and fetal withdrawal must be managed on an individualized basis, taking into consideration the substance of abuse in question, along with maternal or fetal needs. For example, it may not be prudent to withdraw methadone from an addicted or abusing mother because this may increase the likelihood of stillbirth.[59] In contrast, the withdrawal of cocaine will likely diminish the possibility of catastrophic placental abruption or stillbirth. It is best to adopt a team approach regarding maternal and neonatal withdrawal, incorporating a system-based practice model involving neonatologists, psychiatrists, psychologists, and social workers. Preferably, these providers will have some expertise in the management of substance-abusing mothers and their newborns.

CONCLUSION

The opportunities for the abuse of psychoactive substances in pregnancy are vast, and there is evidence that the use and misuse of these substances may be increasing. Tobacco use has a strong association with spontaneous miscarriage, fetal growth restriction, and preterm delivery. Heavy caffeine use may be associated with first-trimester loss. The abuse of alcohol has a significant potential impact on pregnancy, the most important being fetal alcohol spectrum disorder. Heavy use of opioids and sedative-hypnotics may not be strongly associated with

teratogenicity, but fetal sedation and withdrawal at the time of delivery is an extremely unfortunate consequence and the long-term effects of prolonged fetal exposure to these drugs may be potentially concerning. Methadone maintenance clinics are suggested for opiate abusing pregnant patients. Cocaine abuse is strongly associated with fetal growth restriction and potentially catastrophic placental abruption and stillbirth. Amphetamine use may be increasing, particularly in younger mothers, and is associated with poor maternal nutrition and fetal growth restriction. Like most of the other drugs and substances of abuse, marijuana use may also be associated with fetal growth restriction as well.

It remains extremely important to take a careful history when you are caring for patients with potential substance abuse issues and develop a team approach involving individuals with expertise in rehabilitation and the care of mothers and newborns with substance abuse issues. Social workers and neonatologists should be consulted as well, especially at the time of delivery and in the postpartum period. In many instances pregnancy can act as a sentinel event that can help substance-abusing mothers begin to come to terms with their highly self-destructive behaviors, which can also have an unanticipated impact on their unborn or newborn children.

REFERENCES

1. Kuczkowski KM. The effects of drug abuse on pregnancy. Curr Opin Obstet Gynecol 2007; 19:578–85.
2. Office of Applied Studies, Substance Abuse and Mental Health Services Administration. Results from the 2002 National Survey on Drug Use and Health: National findings (DHHS Publication No. SMA 03-3836, NSDUH Series H-22). Rockville, MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies, 2003. [Available at http://www.oas.samhsa.gov/p0000016.htm#2k2].
3. IARC (International Agency for Research on Cancer) Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum 2004; 83:1–1438.
4. Spitzer WO, Lawrence V, Dales R, Hill G, Archer MC, Clark P, Abenhaim L, Hardy J, Sampalis J, Pinfold SP, et al. Links between passive smoking and disease: a best-evidence synthesis. A report of the Working Group on Passive Smoking. Clin Invest Med 1990; 13:17–42.
5. National Institutes of Health State-of-the-Science conference statement: tobacco use: prevention, cessation, and control. Ann Intern Med 2006; 145:839–844.
6. Kandel DB, Griesler PC, Schaffran C. Educational attainment and smoking among women: risk factors and consequences for offspring. Drug Alcohol Depend 2009; 104(Suppl 1):S24–33.
7. Lumley J, Oliver SS, Chamberlain C, Oakley L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev 2004:CD001055.
8. Einarson A, Riordan S. Smoking in pregnancy and lactation: a review of risks and cessation strategies. Eur J Clin Pharmacol 2009; 65:325–30.
9. Goodwin RD, Keyes K, Simuro N. Mental disorders and nicotine dependence among pregnant women in the United States. Obstet Gynecol 2007; 109:875–83.
10. Thielen A, Klus H, Muller L. Tobacco smoke: unraveling a controversial subject. Exp Toxicol Pathol 2008; 60:141–56.
11. Andres RL, Day MC. Perinatal complications associated with maternal tobacco use. Semin Neonatol 2000; 5:231–41.
12. Crawford JT, Tolosa JE, Goldenberg RL. Smoking cessation in pregnancy: why, how, and what next. Clin Obstet Gynecol 2008; 51:419–35.
13. Burton GJ, Palmer ME, Dalton KJ. Morphometric differences between the placental vasculature of nonsmokers, smokers and ex-smokers. Br J Obstet Gynaecol 1989; 96:907–15.
14. Fanslow J, Silva M, Robinson E, Whitehead A. Violence during pregnancy: associations with pregnancy intendedness, pregnancy-related care, and alcohol and tobacco use among a representative sample of New Zealand women. Aust N Z J Obstet Gynaecol 2008; 48:398–404.
15. Rosenberg L, Mitchell AA, Shapiro S, Slone D. Selected birth defects in relation to caffeine-containing beverages. JAMA 1982; 247:1429–32.
16. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Caffeinated and alcoholic beverage intake in relation to ovulatory disorder infertility. Epidemiology 2009; 20(3):374–81.
17. Weng X, Odouli R, Li DK. Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study. Am J Obstet Gynecol 2008; 198:279 e1–8.
18. Hadeed A, Siegel S. Newborn cardiac arrhythmias associated with maternal caffeine use during pregnancy. Clin Pediatr (Phila) 1993; 32:45–7.
19. Briggs G, Freeman R, Yaffe J. Drugs in pregnancy and lactation. Philadelphia: Lippincott Williams & Wilkins, 2008.
20. Floyd RL, Jack BW, Cefalo R, Atrash H, Mahoney J, Herron A, Husten C, Sokol RJ. The clinical content of preconception care: alcohol, tobacco, and illicit drug exposures. Am J Obstet Gynecol 2008; 199:S333–9.

21. Chang G. Alcohol-screening instruments for pregnant women. Alcohol Res Health 2001; 25:204–9.

22. Creasy RK, Resnik R, Iams JD. Creasy and Resnik's maternal-fetal medicine : principles and practice. Philadelphia, PA: Saunders/Elsevier, 2009.

23. Fleming MF, Lund MR, Wilton G, Landry M, Scheets D. The Healthy Moms Study: the efficacy of brief alcohol intervention in postpartum women. Alcohol Clin Exp Res 2008; 32:1600–6.

24. Minozzi S, Amato L, Vecchi S, Davoli M. Maintenance agonist treatments for opiate dependent pregnant women. Cochrane Database Syst Rev 2008:CD006318.

25. Rettig R. Federal Regulation of Methadone: Table of Contents and Executive Summary. Washington, DC: National Academy Press, 1995.

26. Food and Drug Administration. Labelling and prescription drug advertising:content and format for labelling for human prescription drug. Fed Reg 1980; 44:37434–67.

27. NSDUH. Substance Abuse and Mental Health Administration. Results form the 2005 National Survey on Drug Use and Health: National Findings. In: Office of Applied Studies, NSH- Ed. Rockville, MD: DHHS, 2006.

28. Schempf AH, Strobino DM. Illicit drug use and adverse birth outcomes: is it drugs or context? J Urban Health 2008; 85:858–73.

29. Muhuri PK, Gfroerer JC. Substance use among women: associations with pregnancy, parenting, and race/ethnicity. Matern Child Health J 2009; 13:376–85.

30. Bhuvaneswar CG, Chang G, Epstein LA, Stern TA. Cocaine and opioid use during pregnancy: prevalence and management. Prim Care Companion J Clin Psychiatry 2008; 10:59–65.

31. Bateman DA, Chiriboga CA. Dose-response effect of cocaine on newborn head circumference. Pediatrics 2000; 106:E33.

32. Vidaeff AC, Mastrobattista JM. In utero cocaine exposure: a thorny mix of science and mythology. Am J Perinatol 2003; 20:165–72.

33. Bauer CR, Langer JC, Shankaran S, Bada HS, Lester B, Wright LL, Krause-Steinrauf H, Smeriglio VL, Finnegan LP, Maza PL, Verter J. Acute neonatal effects of cocaine exposure during pregnancy. Arch Pediatr Adolesc Med 2005; 159:824–34.

34. Minnes S, Singer LT, Humphrey-Wall R, Satayathum S. Psychosocial and behavioral factors related to the post-partum placements of infants born to cocaine-using women. Child Abuse Negl 2008; 32:353–66.

35. Cox S, Posner SF, Kourtis AP, Jamieson, DJ. Hospitalizations with amphetamine abuse among pregnant women. Obstet Gynecol 2008; 111:341–7.

36. Zapata LB, Hillis SD, Marchbanks PA, Curtis KM, Lowry R. Methamphetamine use is independently associated with recent risky sexual behaviors and adolescent pregnancy. J Sch Health 2008; 78:641–8.

37. Wouldes T, LaGasse L, Sheridan J, Lester B. Maternal methamphetamine use during pregnancy and child outcome: what do we know? N Z Med J 2004; 117: U1180.

38. Bateman DN, McElhatton PR, Dickinson D, Wren C, Matthews JN, O'Keeffe M, Thomas SH. A case control study to examine the pharmacological factors underlying ventricular septal defects in the North of England. Eur J Clin Pharmacol 2004; 60:635–41.

39. Werler MM, Sheehan JE, Mitchell AA. Association of vasoconstrictive exposures with risks of gastroschisis and small intestinal atresia. Epidemiology 2003; 14:349–54.

40. Thomas DB. Cleft palate, mortality and morbidity in infants of substance abusing mothers. J Paediatr Child Health 1995; 31:457–60.

41. Bays J. Fetal vascular disruption with prenatal exposure to cocaine or methamphetamine. Pediatrics 1991; 87:416–8.

42. Nora JJ, Vargo TA, Nora AH, Love KE, McNamara DG. Dexamphetamine: a possible environmental trigger in cardiovascular malformations. Lancet 1970; 1:1290–1.

43. Heinonen OP, Sloan D, Shapiro S. Birth defects and drugs in pregnancy. Littleton, MA: Publishing Sciences Group Inc., 1977.

44. Little BB, Snell LM, Gilstrap LC 3rd. Methamphetamine abuse during pregnancy: outcome and fetal effects. Obstet Gynecol 1988; 72:541–4.

45. Milkovich L, van der Berg BJ. Effects of antenatal exposure to anorectic drugs. Am J Obstet Gynecol 1977; 129:637–42.

46. Smith LM, LaGasse LL, Derauf C, Grant P, Shah R, Arria A, Huestis M, Haning,W, Strauss A, Della Grotta S, Liu J, Lester BM. The infant development, environment, and lifestyle study: effects of prenatal methamphetamine exposure, polydrug exposure, and poverty on intrauterine growth. Pediatrics 2006; 118:1149–56.

47. Naeye RL. Maternal use of dextroamphetamine and growth of the fetus. Pharmacology 1983; 26:117–20.

48. Ramin SM, Little BB, Trimmer KJ, Standard DI, Blakely CA, Snell LM. Methamphetamine use during pregnancy. Am J Obstet Gynecol 1992; 166:353.

49. Oro AS, Dixon SD. Perinatal cocaine and methamphetamine exposure: maternal and neonatal correlates. J Pediatr 1987; 111:571–8.

50. Smith L, Yonekura ML, Wallace T, Berman N, Kuo J, Berkowitz C. Effects of prenatal methamphetamine exposure on fetal growth and drug withdrawal symptoms in infants born at term. J Dev Behav Pediatr 2003; 24:17–23.

51. Skelton MR, Williams MT, Vorhees CV. Developmental effects of 3,4-methylenedioxymethamphetamine: a review. Behav Pharmacol 2008; 19:91–111.

52. Abel EL, Sokol RJ. Marijuana and cocaine use during pregnancy. Philadelphia: Lea & Febiger, 1988.

53. Chasnoff IJ, Landress HJ, Barrett ME. The prevalence of illicit drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Phila County, Florida. N Engl J Med 1990; 322: 1202.

54. National Institute on Drug Abuse (NIDA) Research Report Series: Marijuana Abuse. July 2005. NIH Publication Number 05-3859.

55. Hatch EE, Bracken MB. Effect of marijuana use in pregnancy on fetal growth. Am J Epidemiol 1986; 124:986–93.

56. Greenland S, Richwald GA, Honda GD. The effects of marijuana use during pregnancy. II. A study in a low-risk home-delivery population. Drug Alcohol Depend 1983; 11:359–66.

57. Linn S, Schoenbaum SC, Monson RR, Rosner R, Stubblefield PC, Ryan KJ. The association of marijuana use with outcome of pregnancy. Am J Public Health 1983; 73:1161–4.

58. Shiono PH, Klebanoff MA, Nugent RP, Cotch MF, Wilkins DG, Rollins DE, Carey JC, Behrman RE. The impact of cocaine and marijuana use on low birth weight and preterm birth: a multicenter study. Am J Obstet Gynecol 1995; 172:19–27.

59. American College of Obstetricians and Gynecologists. Guidelines for Perinatal Care, Sixth Edition. Atlanta, GA: ACOG, 2007.

60. Byrne MW, Lerner HM. Communicating with addicted women in labor. MCN Am J Matern Child Nurs 1992; 17:22–6.

61. Kuczkowski KM. Labor analgesia for the tobacco and ethanol abusing pregnant patient: a routine management? Arch Gynecol Obstet 2005; 271:6–10.

62. Ludlow J, Christmas T, Paech MJ, Orr B. Drug abuse and dependency during pregnancy: anaesthetic issues. Anaesth Intensive Care 2007; 35:881–93.

63. Kuczkowski KM. Anesthetic implications of drug abuse in pregnancy. J Clin Anesth 2003; 15(5):382–94.