Management of Addiction Disorders in Pregnancy

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Abstract: In this article, we will review the prevalence of addiction disorders in pregnancy and the impact that it has on perinatal morbidity and mortality. We will then review effective screening techniques and propose a management scheme for achieving short-term abstinence leading to the ultimate goal of long-term recovery. The various medical and obstetric complications unique to this patient population will be discussed as well as the specific adverse effects of substance abuse on placentation and the developing fetus. Finally, medications proven efficacious in the treatment of addiction disorders will be reviewed in the context of their use in the pregnant population.

Key Words: pregnancy, pregnancy complications, fetus, newborn, addiction opiate dependence, substance dependence, alcohol dependence, cocaine, methamphetamine, human, review

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Pregnancy presents unique challenges to the physician caring for patients with addiction disorders. The negative social stigma associated with addiction is amplified toward this population. As a consequence, pregnant women are frequently demonized for abusing drugs. Indeed, many states have criminalized this behavior, subjecting these patients to prosecution and incarceration without adequate treatment.[1] Furthermore, obstetric care providers often lack the ability to effectively screen their patients for substance abuse,[2,3] and negative attitudes toward these patients frequently limit their access to adequate prenatal care. Because of this negative social stigma and the consequences thereof, many women react with shame and attempt to conceal their drug use. The resultant perinatal morbidity and mortality rates are unacceptably high.[4–7]

The role of illicit drug use in the transmission of human immunodeficiency virus (HIV) is undisputed. The pregnant woman engaging in illicit drug use also is at risk for increased morbidity and mortality associated with other parallel high-risk behaviors, including violence,[8] transmission of hepatitis B and hepatitis C viruses, and other sexually transmitted infections. Nutritional deficiencies, repeated episodes of withdrawal, and direct drug effects on utero-placental perfusion lead to fetal growth deficiencies, preterm labor, fetal death in utero, and other pregnancy complications.

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HOW PREVALENT IS DRUG USE IN PREGNANCY?

Significant differences exist between men and women who are affected by addiction disorders with respect to the emotional turmoil that leads to the substance abuse and the psychologic factors that predispose them to become addicted. Many women experience intolerable stress from lack of social power.[9] They are forced to conform to a stereotyped, subordinate "sex role," which leads them to substance abuse. These women receive the message in early life that they are less worthy because they are women. The women who subsequently develop addiction disorders are then stigmatized more harshly by society because of their gender. They frequently find themselves in abusive relationships and are more likely than men to have been victims of childhood physical[10] and sexual[11,12] abuse. Kendler and colleagues[12] demonstrated in studies of female twins that a woman is 6 times more likely to develop a drug addiction and 4 times more likely to develop alcoholism if she was sexually abused as a child. In twins discordant for sexual abuse, addiction disorders were consistently more prevalent in the abused sibling. Major depression seems to be a more frequent comorbid antecedent diagnosis in women who develop addiction disorders than in men.[13] The depression seems to be the result of sex-specific genetic and environmental factors and does not seem to arise from the same factors underlying substance abuse disorders in men.

Women also are more likely than men to abuse prescription drugs.[14,15] The most commonly abused medications include benzodiazepines, hydrocodone bitartrate (Vicodin), and Fiorinal (Butalbitol, caffeine, and aspirin). Doctor shopping is common and the abuse of medications is generally for self-treatment of comorbid conditions. This form of chemical coping[16] includes the use of prescription stimulants for weight control and opiates to overcome depression or other forms of emotional pain.[17]

In the United States, men are more likely to use, abuse, and be dependent on alcohol or illicit drugs than women.[18] In 2003, approximately 4% of married women aged 18 to 49 years were dependent on or abusing alcohol or an illicit drug compared with 11% of those who were divorced or separated and 16% who had never been married. Among men in the same age range, 10% of those who were married were dependent on or abusing alcohol or an illicit drug compared with 23% of divorced or separated and 24% who had never

been married. However, comparable rates of alcohol, tobacco, marijuana, cocaine, and heroin use are seen among adolescents.[19] These results are of particular concern in light of the finding by Greenfield and colleagues[20] that women have a heightened vulnerability to the physical, mental, and social consequences of substance use.

Currently, women have an estimated lifetime prevalence of 17.9% and a 12-month prevalence of 6.6% for any substance abuse disorder (excluding nicotine dependence).[19] Epidemiologic studies on the prevalence of specific drug use in pregnancy are lacking; however, some studies have reported on the overall frequency of illicit drug use in pregnancy. The National Study on Drug Use and Health (NSDUH) is a continuation of the National Household Survey on Drug Abuse. The update for 2002 and 2003 on substance abuse in pregnancy[21] demonstrated that 4.3% of pregnant women aged 15 to 44 years had used an illicit drug during the past month compared with 10.4% of nonpregnant women in the same age category (Fig. 1). The prevalence of substance abuse was highest among nonpregnant white women. Among the pregnant women, past month illicit drug use was greatest in the African American population. Substance abuse was lowest in both pregnant and nonpregnant Hispanic women.

In women who had delivered within the previous 12 months, the rates of past month illicit drug use was lower than among the other nonpregnant women (8.4% vs. 10.6%). It remained higher than in the pregnant group (4.3%). Although this was a cross-sectional study, these data at least suggest that reproductive-aged women tend to increase their substance use during the year after giving birth. In this study, younger pregnant women, those aged 15 to 25 years, were more likely to have used an illicit drug during the past month than older women, aged 26 to 44 years. Other studies utilizing various methods, including neonatal meconium testing, urine toxicology at the initial prenatal visit, and patient interviews, have estimated that the prevalence of illicit drug use during pregnancy varies from 0.4% to 27%.[22–25]

The NSDUH update on substance abuse showed a decline in use of illicit drugs, alcohol, and tobacco during pregnancy (Fig. 2). This finding suggests that although women did not discontinue their dependence completely during pregnancy, this may be an invaluable opportunity to screen, educate, and refer these patients for treatment.

SCREENING FOR SUBSTANCE ABUSE DISORDERS IN PREGNANT WOMEN

Most obstetric care providers fail to adequately screen their patients for substance abuse disorders.[2] This stems from a multitude of reasons, the most prevalent of which include: 1) refusal to accept addiction as a disease; 2) lack of knowledge of treatment options; 3) disbelief that substance abuse disorders are prevalent among their patients; 4) reservations about the efficacy of treatment programs; and 5) concern about liability should a substance abuse disorder be identified. This last reason is a major obstacle. An act of omission (failure to refer for appropriate treatment) may be cause for civil legal action should the pregnancy outcome be less than perfect. Furthermore, many states have mandatory reporting requirements when a substance abuse disorder is identified. Failure to comply can result in penalties ranging from monetary fines to disciplinary action against their medical license. It is the physician's responsibility to be aware of the reporting requirements in his/her respective state and remain in compliance with the law. In Virginia, no specific law requires reporting a pregnant woman with a substance abuse disorder; however, all licensed practitioners must, as a routine component of prenatal care, establish and implement a medical history protocol to *screen* all pregnant patients for substance abuse to determine the need for further evaluation. To preserve the trust between patient and physician, the results of

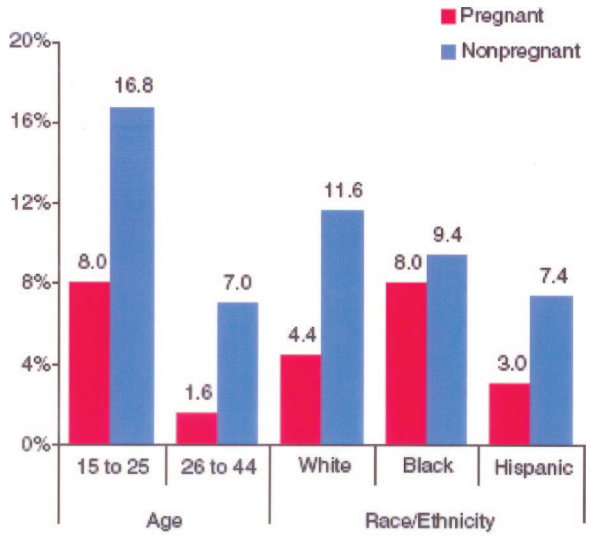

FIGURE 1. Percentages of past-month illicit drug use among women aged 15 to 44 years by pregnancy status, age, and race/ethnicity. From the Office of Applied Studies, 2005.

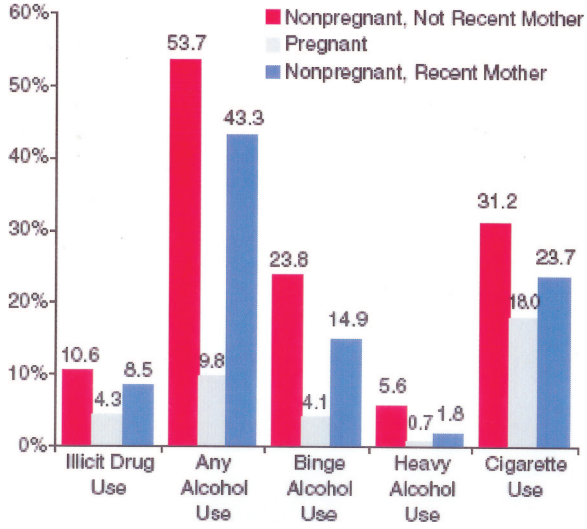

FIGURE 2. Percentages among women aged 15 to 44 years who reported past-month substance use by pregnancy and recent motherhood status: 2002 and 2003. From the Office of Applied Studies.

the medical history screen and/or substance abuse evaluation may not be admissible in any criminal proceeding (§54.1-2403.1 of the Code of Virginia). Unfortunately, this statute is largely unenforceable and most obstetric care providers are unaware of the law. The reporting requirements are more stringent for the pediatric care providers. Section §63.2-1509 of the Code of Virginia requires that attending physicians report to local social services departments, or the Child Abuse and Neglect Agency, all newborns medically diagnosed for exposure to alcohol or nonprescription drugs during pregnancy. Failure to report could result in criminal liability punishable as a misdemeanor with an imposed fine. One of the roles of addiction medicine physicians is to educate the health care providers in their local communities on the disease model of addiction, reporting requirements, and the various screening techniques available.

For screening to be effective, the procedure should be brief and simple to incorporate into daily clinical practice. The attitude of the interviewer is more important than the specific questions being asked. A woman with an addiction disorder will immediately take note of any judgmental tone or affect in the health care provider, and her guilt and shame regarding drug or alcohol use will cause her to deny or refuse to disclose her history. Also, it is best to begin the process with questions perceived to be less threatening to the patient, such as questions about family history of substance abuse. The more pointed questions should be reserved for later in the interview after a rapport has been developed with the patient. Patients who have multiple risk factors for substance abuse should draw particular attention. Studies have identified several risk factors associated with perinatal substance abuse. These include depression,[13,26] childhood sexual abuse,[11,12] homelessness,[26,27] family history of substance abuse,[28] inadequate social support,[26] past use of alcohol and tobacco,[3] and age.[21] Chasnoff and collegues[25] applied this technique in their study of 2002 pregnant women from 9 prenatal clinics in South Carolina and Washington state. They found that women who drank in the month before pregnancy were approximately 41 times more likely to currently use drugs or alcohol or both than women who had never drank alcohol. They also were approximately 5 times more likely to currently use drugs or alcohol or both than women who did not use alcohol in the month before pregnancy but who had used alcohol in the past. Similarly, women who smoked in the month before pregnancy were approximately 9 times more likely to currently use drugs or alcohol or both than women who had never smoked. They were approximately 2 times more likely to currently use drugs or alcohol or both than women who did not smoke in the month before pregnancy but who had smoked in the past. They found that the majority of current substance abusers could be identified by asking 3 simple questions at the prenatal visit:

1. Have you ever drank alcohol?
2. How much alcohol did you drink in the month before your pregnancy?
3. How many cigarettes did you smoke in the month before your pregnancy?

Thus, a clinical profile can be developed identifying those at highest risk for substance abuse during pregnancy. The clinical characteristics and the associated relative risk for substance abuse are shown in Table 1. Those women deemed at high risk for substance abuse should then be referred for a comprehensive assessment by a multidisciplinary team trained to identify substance abuse disorders. This should be done as a second-level procedure outside the primary or obstetric care provider's facility and include an in-depth evaluation addressing not only the substance abuse but the personal and psychosocial issues that would otherwise complicate the pregnancy. It is unrealistic to assume successful intervention for substance abuse without having adequate services to assist the patient in dealing with the legal, financial, and psychosocial consequences of drug use. Such programs are available in most communities through the departments of social services but are underutilized by obstetric care providers. It is incumbent upon the addiction specialist, therefore, to assist in the identification of these patients and make the appropriate referrals. Admission to residential or intensive outpatient treatment has been demonstrated to be cost-effective and result in improved outcomes for the mother and fetus. Svikis and colleagues[29] demonstrated higher birth weights and higher gestational age at delivery and reduced rates neonatal ICU admissions in women who were engaged in a multidisciplinary treatment program at the time of delivery compared with those who were not in treatment. They also showed an overall cost savings of $4644 per mother–infant pair. Finally, as with any chronic disease, a long-term, evidence-based, medical management model is needed to ensure the highest likelihood for sustained recovery.

MEDICAL COMPLICATIONS

Both the use of illicit drugs during pregnancy and the associated high-risk behaviors contribute to medical complications. Table 2 lists the complications seen with increased frequency in gravidas with addiction disorders.

Anemia is common to all pregnancies. As part of the normal physiologic response to pregnancy, blood volume increases by 50%, whereas red cell mass increases by only 30%. Therefore, a mild anemia with normal red cell indices is expected and is referred to as "dilutional" anemia. This, of course, requires no further evaluation. Severe anemia (Hgb < 9, Hct <28) with abnormal red cell indices does require a workup. Microcytic anemia may be nutritional (iron-deficiency) in nature or may indicate the presence of an hemoglobinopathy. Macrocytic indices suggest a B_{12} or folate deficiency.

It should be noted that in patients who are HIV-positive, anemia has a significant impact on the clinical outcomes of quality of life and overall prognosis.[30] In these patients, anemia has been shown to be a statistically significant predictor of progression to the acquired immunodeficiency syndrome and is independently associated with an increased risk of death. Treatment of anemia with epoetin-alpha[31] has resulted in a significant reduction in the numbers of patients requiring transfusions and the mean number of units of blood transfused. Resolution of anemia has resulted

TABLE 1. Factors Correlated with Alcohol or Drug Use During Pregnancy

	Adjusted Odds Ratio	
Characteristic	**Alcohol or Drug Use**	**Drug Use Only**
Ever smoked cigarettes	6.03* (0.003)	4.06† (0.038)
Ever drank alcohol	7.68* (0)	4.53* (0.009)
Ever drank alcohol and ever smoked cigarettes	0.18* (0.004)	0.22† (0.018)
Smoked cigarettes during month before pregnancy	1.53 (0.176)	2.62† (0.034)
Drank alcohol during month before pregnancy	5.39* (0)	2.43* (0.003)
Another adult in household uses illicit drugs or substantial alcohol	1.39 (0.175)	1.77† (0.041)
Another adult in household has been in treatment for drug or alcohol abuse	1.21 (0.502)	1.17 (0.642)
Moderate or severe depression	1.55† (0.046)	2.37* (0.001)
Occasionally has crying spells (during past week)	1.03 (0.902)	1.34 (0.31)
Occasionally felt blue (during past week)	0.98 (0.949)	0.83 (0.525)
First pregnancy	1.5 (0.097)	1.21 (0.53)
Has a child who lives in another household	1.33 (0.387)	0.8 (0.608)
Lives alone or with small children	1.93† (0.014)	1.74 (0.098)
Homeless during past 3 years	1.53 (0.1)	1.52 (0.16)
No usual source of health care	1 (0.994)	1.3 (0.282)
Worried about pregnancy	1.38 (0.108)	1.03 (0.894)
Age (yr)		
20–25	0.98 (0.94)	0.66 (0.158)
>25	1.23 (0.507)	0.77 (0.493)

Sample size is 1949.
*Significantly different from 1 at $P = 0.01$ level, 2-tailed test.
†Significantly different from 1 at $P = 0.05$ level, 2-tailed test.
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in improved quality of life, physical functioning, energy, and fatigue in individuals with HIV.[30] More recently, the use of highly active antiretroviral therapy (HAART) has been associated with a significant increase in hemoglobin concentrations and a decrease in the prevalence of anemia.[32] Combination therapy, including (HAART), seems to be safe to use at any time during pregnancy.[33] Pregnancy per se has no detrimental influence on the progression of HIV nor does it affect the response to treatment.

There is a strong relationship between depression and substance abuse. Therefore, it is not surprising that one might encounter depression with increased frequency when caring for pregnancies complicated by addiction disorders. Indeed, substance abuse, violence, and depression are so closely interrelated in this population that the prenatal patient who gives a history of any one of these should be carefully evaluated for the presence of the other two.[34]

Since the introduction of selective serotonin reuptake inhibitors (SSRI) into clinical practice, their use has become widespread in pregnant women. Recently, concern regarding the safety of these agents has arisen. Although several investigators have failed to find an increased risk of major congenital malformations associated with the use of SSRIs during pregnancy,[35–37] GlaxoSmithKline described 2 recent unpublished reports from a Swedish national registry and a U.S. insurance claims database that have raised concerns about an increased risk of congenital cardiac malformations (atrial and ventricular septal defects) associated with first trimester exposure to the SSRI paroxetine (Paxil).[38] The U.S. Food and Drug Administration in 2005 issued a public health advisory regarding the use of paroxetine during pregnancy, and the manufacturer changed paroxetine's pregnancy category from C to D.[39] Late-term use of SSRIs has been associated with neonatal abstinence syndrome (NAS).[40,41] Other pregnancy complications include low birth weight, fetal death, neonatal seizures, preterm birth,[35] and persistent pulmonary hypertension.[42] Although these adverse outcomes have been reported in association with a wide variety of SSRIs, the relationship seems to be strongest with paroxetine.[41,42]

The American College of Obstetricians and Gynecologists have published a Committee Opinion[43] recommending that treatment with all SSRIs or selective norepinephrine reuptake inhibitors or both during pregnancy be individualized and, if possible, paroxetine use among pregnant women or women planning to become pregnant be avoided. Any woman exposed to paroxitine during the first trimester should be referred for a fetal echocardiogram. Initiation or continuation of an SSRI during pregnancy should be done only after carefully weighing the risks and benefits and with well-documented, informed consent. Given the high risk for relapse in gravidas with addiction disorders and comorbid depression, the use of an SSRI may well be justified. Although data are lacking at

TABLE 2. Medical Complications Common to Pregnancy and Substance Abuse

Anemia
Bacteremia/sepsis
Endocarditis
Cellulitis
Depression/anxiety
Gestational diabetes
Hepatitis (chronic and acute)
Hypertension/tachycardia
Phlebitis
Pneumonia
Gingivitis/poor oral hygiene
Sexually transmitted diseases
Chlamydia
Gonorrhea
Condyloma accuminata
Herpes
HIV/AIDS
Syphilis
Tetanus
Cystitis
Pyelonephritis

this time, one should consider weaning the SSRI late in the third trimester in an attempt to mitigate the severity of NAS. Because the medication is excreted in breast milk, breastfeeding may contribute to a decrease in the observed NAS.[44] The highest risk of reemergence of depression occurs during the immediate postpartum period. If the SSRI was discontinued during the pregnancy, it should be restarted on the first postpartum day. All patients should be closely followed in the weeks after delivery and adjunctive therapy added if and when necessary.

The infectious complications encountered in pregnancy are largely the result of parallel high-risk behaviors and can be minimized by control of the addiction and intense psychosocial support. Sexually transmitted diseases are common because the women prostitute themselves for drugs or otherwise engage in sex with multiple partners. Intravenous drug users are at particularly high risk for hepatitis and HIV. The addiction specialist needs to know that, although obstetric care providers routinely test for hepatitis B, HCV is not a part of a routine prenatal laboratory panel. All patients with addiction disorders should be tested for HCV as well. If positive, referral to a hepatologist is indicated. However, treatment should be deferred until after pregnancy because liver biopsy is potentially hazardous during gestation and the medical treatments are contraindicated during the pregnancy. Liver function tests should be followed closely.

Vertical transmission of HCV to the fetus is relatively inefficient (2.4-7%)[45–47] but is significantly enhanced in women coinfected with HIV.[46] Cesarean delivery does not seem to be protective[47,48]; however, disagreement is seen in the contemporary literature.[49,50] A recent review in the Cochrane Database[51] suggests that the available data are insufficient to comment on this issue. In short, more prospective, randomized trials are needed before elective cesarean delivery can be advocated to prevent vertical transmission of HCV. However, all published reports to date indicate there is no evidence to suggest that breastfeeding is a mode of transmission. The American Academy of Pediatricians and the Centers for Disease Control support breastfeeding in these women; however, it may be prudent for mothers who are HCV-infected and who choose to breastfeed to consider abstaining from breastfeeding if their nipples are cracked and bleeding.

OBSTETRIC COMPLICATIONS

Obstetric complications seen as a consequence of continued illicit drug use can occur slowly over time, as in the development of fetal growth restriction, or can be abrupt in onset, quite spectacular, and immediately life-threatening, as with severe placental abruptions or acute myocardial infarctions resulting from cocaine abuse. In some cases, the effects on the fetus are not seen until early childhood when developmental and cognitive delays are noticed as a potential consequence of benzodiazepine exposure.[52] Prevention of these complications requires close communication between the addiction medicine physician, the obstetric care provider, and the maternal-fetal medicine consultant. Lack of compliance or relapse should be reported by the addictionist and the patient should be brought in for fetal testing. It is our practice at the same time to immediately increase the treatment level in these patients. We also report normal fetal testing and continued compliance to all care providers. Jones and colleagues[53] have shown that compliance in treatment is improved by providing positive reinforcement in the form of an escalating voucher system. We also use positive reinforcement as a technique to maintain compliance.

The major obstetric complications addressed are listed in Table 3. They can be further subdivided by 1 of 2 antecedent pathophysiologic events: hypoxia or inflammation (Figs. 3 and 4). Events leading to hypoxia within the uterine environment are those that adversely affect perfusion of the placenta by the uterine artery. Figure 5 is a schematic representation of a placental unit. Oxygenated, nutrient-rich blood enters the intervillous space through the spiral arterioles branching off the uterine artery. Oxygen and nutrients diffuse

TABLE 3. Obstetric Complications in Gravidas with Addiction Disorders

Placental abruption
Chorioamnionitis
Placental insufficiency
Intrauterine growth restriction
Hypoxic/ischemic brain injury
Meconium passage
Neonatal abstinence syndrome
Spontaneous abortion
Intrauterine fetal death
Premature labor and delivery
Preterm, premature rupture of membranes
Postpartum hemorrhage
Hypertensive emergencies/preeclampsia

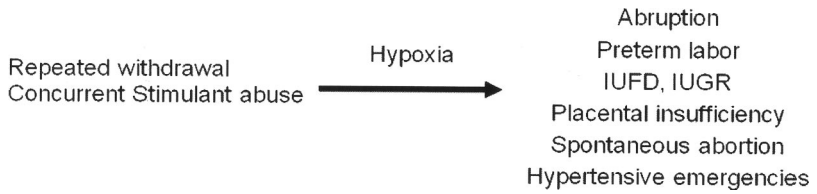

FIGURE 3. Hypoxia-mediated pregnancy complications.

across the villous membrane into the villous capillaries and travel to the fetus. Metabolic and respiratory waste is passed in the opposite direction into the maternal circulation. When maternal perfusion of the uterus is interrupted or severely curtailed, portions of the placenta can undergo separation from the uterus (abruption) or hypoxic death (infarction). These are demonstrated in Figures 6 and 7, respectively.

Placental abruption has many causes and complicates approximately 1% of pregnancies.[54] Risk factors for abruption include previous abruption, smoking, trauma, cocaine use, multifetal gestation, hypertension, preeclampsia, thrombophilias, advanced maternal age, preterm premature rupture of the membranes, and polyhydramnios. The strongest associations have been demonstrated in patients with chronic hypertension and superimposed preeclampsia (odds ratio [OR],[55] 2.8–3.8), cocaine or other stimulant use (OR, 5–10),[56] and tobacco use (OR, 1.6–2.1).[57] An abruption can result in massive hemorrhage with fetal and/or maternal death. Lesser degrees of abruption can be less spectacular but render significant portions of the placenta nonfunctional for the remainder of the pregnancy, thereby limiting fetal access to oxygen and nutrients. Similarly, placental infarctions can result in fetal demise when $>50\%$ of the placental mass is lost or be clinically insignificant when $< 10\%$ of the placental mass is involved. Any sublethal insult to the placenta—abruption or infarction—that limits nutrient and oxygen delivery to the fetus has the potential to limit the fetus' growth. Furthermore, in an environment of chronic hypoxemia, brain development can be compromised, leading to hypoxic-ischemic brain injury.

Although the precise mechanism by which hypoxia can occur in the uteroplacental environment is not known, one possible way is via direct or catecholamine-induced uterine artery spasm. Although the direct effects of stimulants on uterine artery flow in pregnancy have not been studied, cocaine and methamphetamine are strongly catecolaminergic agents and side effects of use include hypertension and tachycardia. Studies on the effects of cocaine on the gravid myometrial cell have demonstrated inhibition of neuronal catecholamine reuptake in the gravid uterus.[58] In an animal model, cocaine has been shown to have a direct effect on enhancing myometrial contractility.[59] In chronically catheterized rats, this effect seemed to be unrelated to the hemodynamic response or pharmacokinetic profile of cocaine. Furthermore, in vitro studies of human myometrial cells have demonstrated that cocaine increases myometrial contractions by both adrenergic and nonadrenergic mechanisms.[60,61]

The increased autonomic response to withdrawal from opiates,[62] benzodiazepines, and alcohol[63] has long been known. Using Doppler velocimetry, maternal cigarette smoking has been demonstrated to cause chronically increased resistances in the maternal uterine, umbilical, and fetal middle cerebral arteries.[64,65] In an earlier study by Koss and colleagues,[66] patients in the second and third trimesters of pregnancy had their uterine artery blood flow measured by Doppler before, during, and for several minutes after the smoking of a standard cigarette. During smoking, there was a velocity reduction within the uterine artery in all subjects. The degree and duration of the reduction in blood flow varied. In most subjects the velocities were approximately 50% of baseline, but a reduction to almost zero was seen in several subjects. Figure 8 shows sample uterine artery Doppler flow wave forms from a normal pregnancy (A) at 32 weeks and an opiate-dependent patient (C) at 34 weeks in moderate withdrawal. This latter patient was noncompliant with treatment and experienced multiple episodes of withdrawal throughout the pregnancy. She delivered a growth-restricted fetus, and the placental pathology confirmed multiple infarctions throughout the parenchyma.

Many of the infectious complications of pregnancy in addicted gravidas lead to inflammatory changes within the uterine decidual tissue and amniotic fluid, which cause increased amounts of interleukin-8, interleukin-6,[67,68] tumor necrosis factor α,[69] and other inflammatory cytokines. These activate production of prostaglandins, metalloprotease, and collagenase enzymes, all of which contribute to premature uterine contractions and digestion of the fetal membranes. Alternatively, the cytokines and prostaglandins produced in the decudual cells can cause preterm contractions and cervical effacement with premature labor as the result. Finally, decidual enzyme production may dominate the process, resulting in membrane digestion and amniorrhexis. Once bacteria gain access to the decidual tissue, a transmembrane migration of the organisms will result in chorioamnionitis.

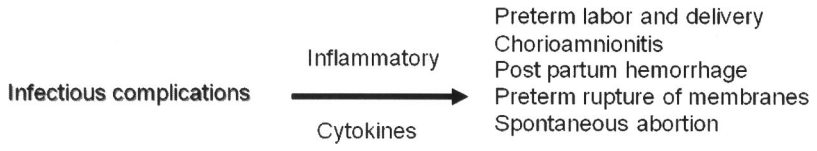

FIGURE 4. Inflammatory cytokine-mediated pregnancy complications.

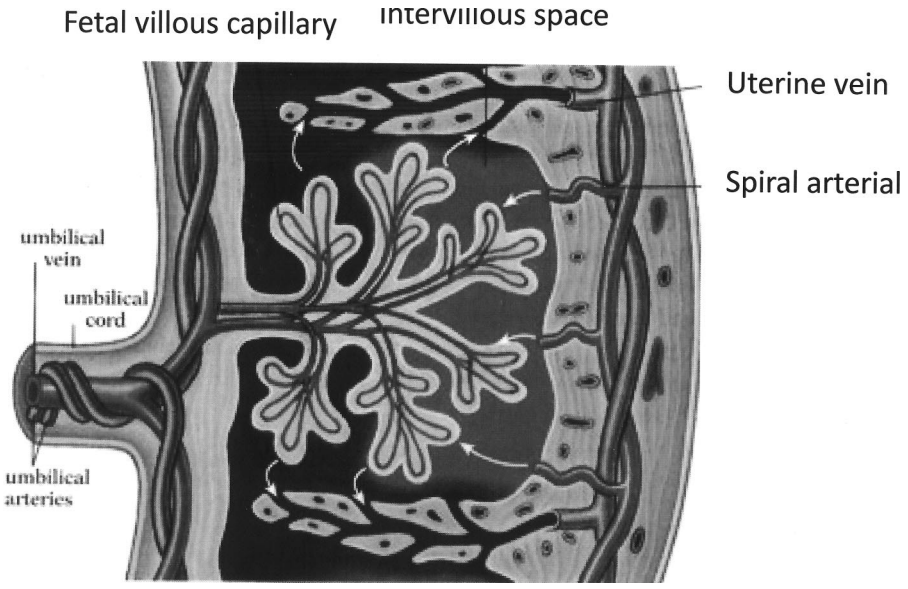

FIGURE 5. Schematic drawing of placental circulation.

These patients will present with fever, uterine tenderness, and contractions. If not promptly treated with antibiotics and delivery, the infection will progress to sepsis and septic shock and death may ensue.

Evidence that drugs of abuse acting through multiple mechanisms (direct, hypoxemia, and inflammatory) result in uterine contractions, cervical dilation, and membrane digestion is supported by the observation that these patients present with advanced cervical dilatation at admission and a shorter latency period to labor and delivery.[70] Further investigations of potential indirect mechanisms of action of drugs of abuse are needed, including altered prostaglandin production, inhibition of beta-adrenergic response, and direct effects on intracellular calcium mobilization for a more complete understanding of the clinical ramifications of drug use during pregnancy.

MEDICAL TREATMENT OF ADDICTION DURING PREGNANCY

In recent years, major advances have been made with respect to medical treatment of addiction disorders. The numbers of medications being made available is unprecedented. Still, obstacles to delivery of these medications to reproductive-age women exist, not the least of which is the reluctance of the pharmaceutical industry to perform clinical trials on this population. The little information that is available on the use of these agents in pregnancy is in the form of case reports or small case series. Taken with the liability issues, women who may become pregnant or those who are pregnant often are denied treatment despite the "greater harm" of continued drug or alcohol use on the developing fetus. There are currently no medications approved by the FDA for treatment of addiction disorders during pregnancy. This does not prevent the practitioner from using a medication "off label" but certain requirements must be met.[71] The patient must meet the diagnostic criteria for dependence. There must be sound scientific evidence to support its use. Evidence of widespread use and support from another qualified clinician are methods of justifying off-label prescribing. An informed consent discussion must be conducted, notifying the patient of the potential risks, anticipated benefits, and alternatives to treatment. Finally, legible documentation of these discussions in the medical records is important.

ALCOHOL ADDICTIONS

Alcohol is a known teratogen that causes a constellation of malformations, including microcephaly, growth deficiency, central nervous system dysfunction, including mental retardation and behavioral abnormalities, and craniofacial abnormalities.[72] Children born with the Fetal Alcohol Spectrum Disorder will have lifelong, serious disability. Whether medical treatment during pregnancy can prevent this devastating outcome remains to be proven. It is incumbent upon the physician caring for these patients to carefully weigh the risks of the medication intended to maintain abstinence against the likelihood of continued alcohol use. The decision of whether to treat is based on the risk benefit analysis.

Benzodiazepines remain the treatment of choice for detoxification during pregnancy. These agents interact with the gamma-aminobutyric acid-A (GABA) receptor, which mediates an increase in inhibitory neurotransmission that counteracts the excitatory state of the brain in alcohol withdrawal. There is some evidence that women may have a greater response to benzodiazepines than men,[73] allowing for reduced dosages. Carbamazepine has been used extensively in Europe for detoxification from alcohol. Several small studies have demonstrated that this agent is most likely as safe and efficacious as the benzodiazepines.[74,75] It has the advantage of having no abuse potential, and it has been widely used in pregnancy for seizure disorders.

However, both agents have been associated with adverse pregnancy outcomes. Despite early reports of facial

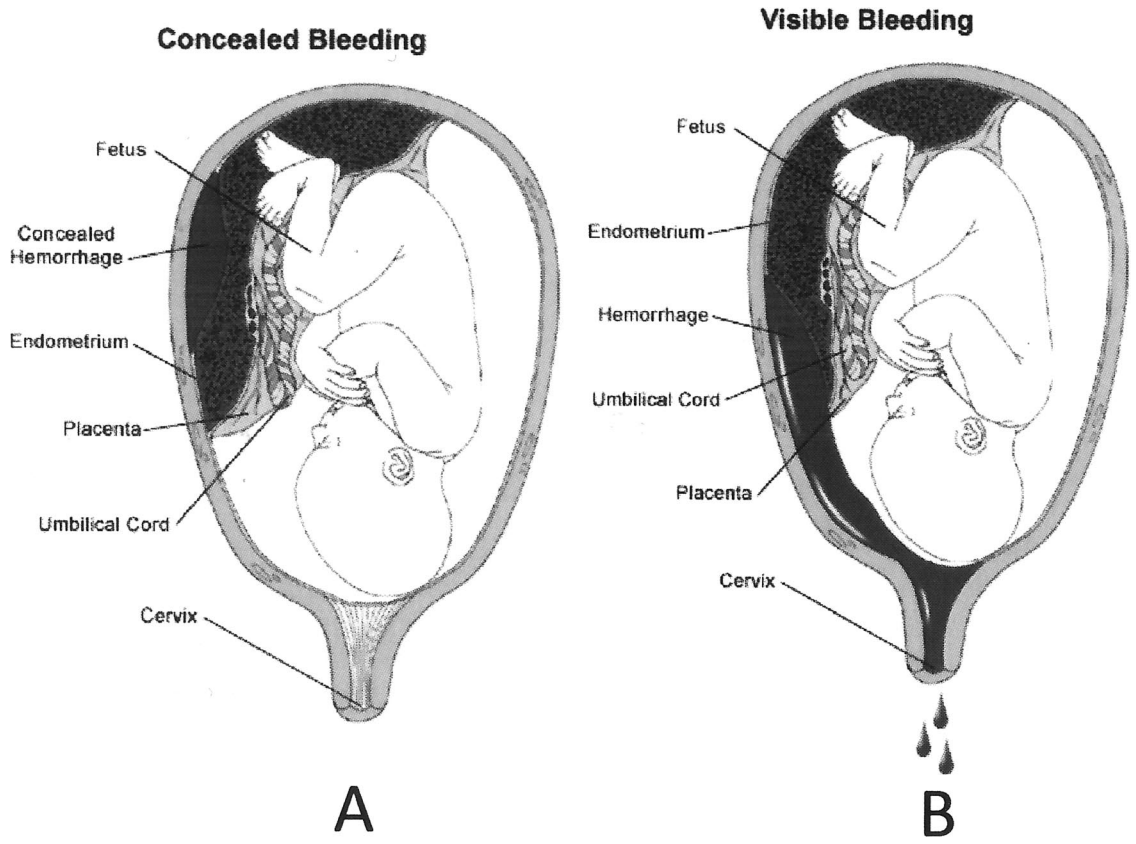

FIGURE 6. Types of abruption. **(A)** Concealed abruption. Blood collects behind the placenta. There is no vaginal bleeding and therefore no overt evidence of the abruption. **(B)** Clinically apparent abruption. Blood tracks between the membranes and escapes through the vagina and cervix. The bleeding can range from scant to massive depending on the extent of the abruption. Figure used by permission from the University of Utah Health Care (http://uuhsc.utah.edu/healthinfo/pediatric/hrpregnant/bleed.htm).

clefts and other fetal anomalies after benzodiazepine exposure, a large study of women whose deliveries were registered by the Medicaid system challenged this position.[76] The investigators identified 80 pregnant women who had received 10 or more benzodiazepine prescriptions during the 4 years of the study. Their records showed heavy general use of health care, frequent alcohol and substance abuse, and other disorders that could confound any effect of the benzodiazepines. Thus, the high rate of teratogenicity after heavy maternal benzodiazepine use occurs when there is multiple alcohol and substance exposure and is not likely the result of benzodiazepine exposure. This finding has been confirmed by other investigators.[77] Benzodiazepines require albumin for serum transport. In the fetus, serum albumin levels are quite low until the third trimester when levels exceed maternal values. Therefore, fetal benzodiazepine levels will remain low during the first and second trimester and increase to those greater than maternal levels during the third trimester. Accordingly, there exists evidence of impaired intrauterine growth, intoxication, and neonatal abstinence syndrome in third-trimester exposed fetuses.[78] Significant differences also were seen in the frequency of perinatal neurobehavior in benzodiazepine-exposed infants compared with controls. First-trimester exposure to Carbamazapine has been associated with an approximately 1-percent risk of neural tube defects.[79] Because this defect may be prevented with maternal administration of folic acid, it is recommended that all pregnant women receiving carbamazapine also receive folate supplementation.[80] The

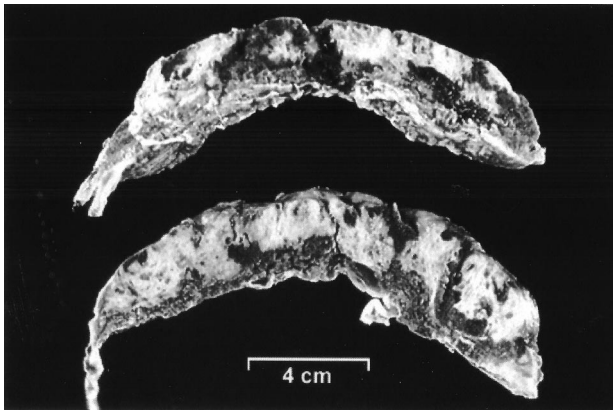

FIGURE 7. Multiple placental infarcts. Gross sections through the central placenta demonstrate infarction of >50% of the placental mass.

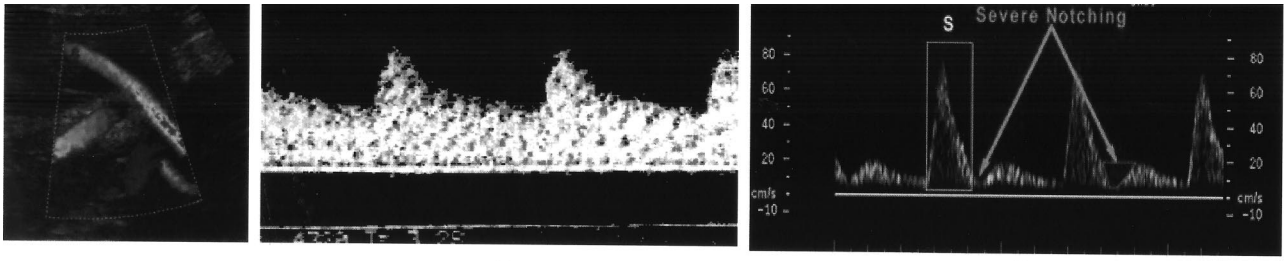

FIGURE 8. Maternal uterine artery Doppler flow studies. **(A)** Maternal uterine artery imaged on color flow mapping as it crosses the internal iliac vessels. **(B)** Normal wave form pattern at 32 weeks. Note the soft systolic peaks and high level of forward diastolic flow. This is consistent with a low resistance, high flow circuit. **(C)** Abnormal wave form from an opiate-dependent patient in moderate withdrawal. Note the high, sharp systolic peak early diastolic notching and low level of diastolic flow. This is consistent with a low flow, high resistance circuit.

efficacy of folic acid in preventing neural tube defects in this particular setting, however, has not been proven. Conversely, studies on adverse neurodevelopment as a consequence of carbamazapine exposure have been reassuring.[81] Given this information, it may be reasonable to use a benzodiazepine for detoxification during the first trimester, reserving Carbamazapine for second and third trimester use.

Disulfiram was approved by the FDA in 1952 for use as a deterrent to relapse in alcohol addiction. It acts by inhibiting aldehyde dehydrogenase, which leads to accumulation of acetaldehyde when alcohol is ingested. The resulting symptoms of the disulfiram-alcohol reaction include facial flushing, tachycardia, hypotension, nausea, vomiting, and general malaise. Although fetal anomalies have been reported in pregnancies exposed to disulfiram, no specific pattern of malformations exists. Furthermore, in all reported pregnancies, exposure to other drugs of abuse, including cocaine, opiates, and alcohol, were noted.[82,83] In the only report to date of isolated disulfiram exposure during the first trimester, Helmbrecht and Abassi[84] observed no anomalies nor were developmental disabilities noted.

Naltrexone and Acamprosate also are available as adjuncts to abstinence in patients with alcohol addiction. Naltrexone was approved by the FDA for treatment of alcoholism in 1994. It is an opiate antagonist and has demonstrated efficacy in reducing alcohol consumption and craving through its blocking of opiate receptor-mediated activation by alcohol of dopaminergic pathways in the brain that are thought to be critical to reward. Limited data on exposure in humans has not indicated any association with anomalies or developmental problems.[85,86] Acamprosate has proven efficacy in decreasing drinking frequency and reducing relapse drinking in abstinent alcoholics. The mechanism of action of acamprosate is obscure, although there is some evidence that it modulates the function of NMDA receptors in brain.[87] Currently, there are no data available on the use of Acamprosate in pregnancy. If a medication is necessary to enhance abstinence during pregnancy, one must weigh the risks of continued alcohol use against the potential teratogenic risks of the medication. Given the available data, Disulfiram or Naltrexone would be the most appropriate choices.

OPIATE ADDICTIONS

As mentioned earlier, opiates are not associated with fetal malformations and the observed adverse pregnancy outcomes are secondary to withdrawal and parallel high-risk behaviors. We now have more than 3 decades of experience with the use of methadone for opiate detoxification and agonist treatment. Long-term abstinence after detoxification is unusual in opiate addiction, and the best results have been demonstrated with continued use of opiate agonist therapy.[88]

Detoxification during pregnancy has been avoided since the 1970s, when there were several reports of associated untoward outcomes. Rementeria and Nunag[89] reported a stillbirth occurring after acute narcotic withdrawal in a term pregnancy. Zuspan et al[90] found increased amniotic fluid epinephrine levels in a woman undergoing a methadone dosage taper. Catecholamine levels stabilized after the dosage was increased. In 1977, these authors recommended avoiding detoxification "unless a scientific means is available to monitor fetal homeostasis." On the basis of reports such as these, physicians are reluctant to detoxify pregnant women, and methadone maintenance has become standard practice. More recently, however, Dasche and colleagues used sonography and fetal heart rate monitoring to assess the safety of detoxification from methadone in 34 otherwise uncomplicated mid trimester pregnancies.[91] Under carefully monitored inpatient conditions, the authors performed a gradual methadone taper. The median maximum dose of methadone was 20 (range, 10–85) mg per day, and the median time to detoxification was 12 (range, 3–39) days. Overall, 20 women (59%) successfully underwent detoxification and did not relapse, 10 (29%) relapsed to opiate use before delivery, and 4 (12%) did not complete detoxification and opted for methadone maintenance. There was no evidence of fetal distress during detoxification, no fetal death, and no preterm deliveries. Two fetuses developed intrauterine growth restriction confirmed after delivery with birth weights less than the fifth percentile. Both infants were born of mothers in the relapse group. Interestingly, 3 of 20 neonates born to mothers who were successfully weaned from methadone required treatment for neonatal abstinence syndrome.

Although detoxification seems to be safe in the second trimester of pregnancy under carefully monitored conditions, relapse to opiate use seems to overshadow any potential benefits. Maas et al[92] described pregnancy outcomes of 75 gravid opiate users, 58 of whom participated in detoxification with methadone. Fifty-six percent of these women relapsed to opiate use after detoxification. Neonatal abstinence syndrome is reported in 15% to 55% of women who undergo successful detoxification in the mid trimester. Despite an ability to detoxify patients during pregnancy, this does not seem to be a practical course to follow except under extraordinary circumstances.

Although methadone is not a teratogen, Rosen and Johnson[93] have raised concern regarding neurodevelopmental delay in methadone-exposed children. They followed a cohort of methadone exposed neonates through 18 months of age. Compared with unexposed controls, the methadone group showed a significantly higher incidence of otitis media, head circumferences below the third percentile, developmental delays, and poor fine motor coordination. These children also had significantly lower scores on the Bayley mental and motor developmental indices. In a more recent prospective, longitudinal-matched cohort study, van Baar and colleagues[94] assessed the neurobehavioral development of 35 infants of drug-dependent mothers with the development of 37 nonexposed control infants. Significantly more infants of drug-dependent mothers than control children had electroencephalograms rated as suspect or abnormal. By the end of the first month, the infants of drug-dependent mothers tended to be more active, and they had worse scores than the controls on the neonatal behavioral assessment scale. The results of these and other studies suggest that even after treatment for the neonatal abstinence syndrome, infants of drug-dependent mothers seem to differ from comparison children, which could indicate later developmental problems. It is difficult, however, to establish what effects are directly attributable to methadone, because many methadone patients in these studies used other drugs and had socioeconomic characteristics that are associated with poor neonatal outcome. Lifschitz and colleagues[95] published conflicting results. They found no significant effect of maternal heroin and methadone use on head growth and neurodevelopmental performance in preschool-aged children. Their data did show an increased incidence of low-average and mildly retarded intellectual performance in the drug-exposed children. However, regression analyses demonstrated that amount of prenatal care, prenatal risk score, and home environment were most predictive of intellectual performance and that the degree of maternal narcotic use was not a significant factor. In a particularly insightful study of the neurodevelopmental consequences of methadone exposure, Hans[96] showed that methadone-exposed infants reared in extremely poor environmental circumstances showed much delayed mental development. Indeed, they seemed to function more poorly than nonexposed infants reared in similar environments and more poorly than methadone-exposed infants reared in more adequate environments. These findings suggest that in the cognitive domain, methadone may not cause a behavioral deficit but instead create a vulnerability in these children that then makes them more susceptible to impoverished environments. Therefore, preventive interventions that focus both on enriching the early experiences of such children and improving the quality of the home environment are likely to be particularly effective.

Controversy exists among methadone providers regarding dosing regimens. Concern regarding the occurrence of neonatal abstinence has resulted in a lowering of methadone dose during pregnancy in many clinics. Dashe and colleagues,[97] in a retrospective cohort study, demonstrated a dose-dependent relationship with the incidence and severity of NAS. The doses of methadone used in this population (20–40 mg per day) were below blocking levels. This has been associated with poor compliance with treatment, high rates of IUGR and prematurity, and correspondingly, a high incidence of polysubstance abuse.[98] McCarthy and colleagues[99] subsequently published on high- versus low-dose methadone maintenance therapy. In this report, high doses of methadone (>100 mg) were not associated with increased risks of neonatal abstinence symptoms but had a beneficial effect on maternal drug abuse. Thus, the dose of methadone used should be individually assessed based on the presence of symptoms of withdrawal and craving. Reducing the dose during pregnancy will only increase the likelihood of relapse, thereby increasing the probability of adverse pregnancy events. To the contrary, because methadone has a wide volume of distribution, significant dose *increases* are expected as the body mass and fluid volume increases during the second and third trimesters. Given the rapid decline in intravascular volume after delivery, our practice is to decrease the dose by 20% to 40% during the immediate postpartum period.

Methadone dosing is frequently split based on little evidence of improved outcome. Data exist demonstrating a higher elimination rate constant (k) and lower half-life compared with nonpregnant controls;[100] however, there are no studies that demonstrate that splitting the dose actually improves pregnancy outcome. DePetrillo and Rice[101] have shown an improvement in program compliance with split dosing, however. Splitting the methadone dose is, therefore, reasonable provided that the patient is not at risk for diversion.

Fetuses exposed to methadone during the third trimester will have a higher rate of abnormal fetal testing. The challenge to the obstetric care provider is to determine which of the abnormal tests represent false-positive results and which deserve intervention. The most common test of fetal well being used in the third trimester is the non-stress test (NST). Methadone causes a higher false-positive or nonreactive rate in the NST particularly if performed 1 to 3 hours after a dose.[92–104] In these instances, a biophysical profile should be performed as a follow-up or primary test. It should be noted that fetal breathing movements also will be decreased as a consequence of methadone.[105]

Doppler studies of the umbilical artery and middle cerebral artery are helpful adjuncts to tests of fetal well-being. The former will indicate the degree of placental vascular resistance caused by previous infarction or intervillous

space thrombosis, and the latter will provide valuable information regarding the placenta's ability to deliver adequate oxygen to the fetus. In cases of sublethal placental injury, the systolic:diastolic ratio and pulsitility index measured in the umbilical artery will increase as resistance to flow within the placental vasculature increases. With more severe placental dysfunction, diastolic blood flow will decrease or disappear altogether, thus increasing these values. In the end stage, preterminal condition, reversal of diastolic flow is seen. As fetal oxygenation declines with declining placental function, the fetus responds by shifting cardiac output to favor cerebral flow at the expense of decreasing flow to the splanchnic bed, including bowel and kidneys. Thus, a trend of increasing resistance in the umbilical artery, decreasing resistance in the middle cerebral artery, and declining amniotic fluid volume provides compelling evidence of declining placental function and identifies the fetus that will require closer testing and may need early delivery to prevent hypoxic-ischemic brain injury.

Whether to encourage breastfeeding in methadone-treated mothers varies significantly by institution. Methadone is transferred to breast milk.[106,107] Some investigators have reported the quantities to be sufficient to prevent or ameliorate withdrawal symptoms in symptomatic infants,[107–109] but based on a more detailed analysis of the methadone levels in breast milk, other investigators have questioned this conclusion.[110,111] Milk:plasma ratios ranging from 0.83[112] to values as low as 0.24[111] have been reported. One estimate of the relative infant dose of methadone (with consideration of the 50-50 mixture of R and S isomers normally in methadone) was 2.8% of the maternal dose.[111] The American Academy of Pediatrics and the WHO Working Group on Human Lactation classified methadone as compatible with breastfeeding.[113,114] Given the overwhelming benefit of breastfeeding in promoting the mother-infant bond, we believe that breastfeeding should be strongly encouraged in these at-risk parents provided no other contraindication, such as maternal HIV infection exists. As a precaution, all mothers should be warned to seek medical advice if their exposed infant appears sedated.[113]

Buprenorphine is an opioid analgesic similar to morphine but with greater potency and with agonist-antagonist properties. It is marketed in IV form as Buprenex and in an orally administered formulation as Subutex. Suboxone is a combination drug containing buprenorphine and naloxone. Naloxone is not active if taken orally or sublingually but will precipitate a withdrawal state if injected intravenously. This property along with the "ceiling effects" on euphoria and respiratory suppression contributes to the safety profile limited abuse potential of the drug. Indeed, it antagonizes the respiratory depression produced by anesthetic doses of fentanyl about as well as does naloxone without completely reversing other opioid effects, such as analgesia.[115] Compared with methadone, the abuse potential is markedly lower, which allows for its use in an outpatient office setting. Because buprenorphine has an extremely high binding affinity for the mu receptor, only limited euphoric effects result when a patient relapses to an illicit opiate. As expected, Subutex and Suboxone have well-documented efficacy as alternatives to methadone for the treatment of opioid addiction in the general population.

Well-controlled studies of the safety and efficacy of Buprenorphine in pregnancy are lacking. From the limited data available, it does not seem to be teratogenic in humans[116] or animals.[117] Administered in monotherapy form as Subutex, it has been used successfully in opioid-dependent pregnant women as a maintenance replacement opioid.[118–124] A 2003 review of the available clinical studies has been published covering approximately 300 pregnancies.[125] Compared with methadone, a lower incidence of NAS has been reported in buprenorphine-exposed neonates. The severity of NAS is reduced as assessed by total opiate required to treat and length of hospital stays. Some data suggest that the placental transfer of this opioid may be limited in comparison with others, such as methadone, thereby limiting fetal exposure and the development of dependency.[126] Deshmukh and colleagues[127] have demonstrated that a large proportion of buprenorphine is metabolized to Norbuprenorphine, the only metabolite formed as determined by high-performance liquid chromatography and mass spectrometry, by placental aromatase (CYP 19) within the microsomal fraction of the trophoblast.

There is a paucity of information available on breastfeeding. Small amounts of buprenorphine are excreted in breast milk. In one study, the estimated daily dose of this agent to the newborn of a mother taking 4 mg per day was 3.3 μg per day.[128] Because buprenorphine is not active if swallowed, it would not be anticipated to have any adverse effects on the neonate. It probably has little pharmacologic effect because no withdrawal signs have been noted when maternal feeding is later abruptly interrupted.[128] Specific studies beyond case reports on this agent are lacking. Breastfeeding can and should be encouraged in this group of patients with appropriate informed consent.

Despite its potential advantages over methadone, buprenorphine is not approved by the FDA for use in pregnancy and any such use is considered "off label." It should be noted that there are no studies that evaluate possible long-term effects on the behavior and neurodevelopment of exposed human infants. Methadone, therefore, remains the "gold standard" for maintenance therapy during pregnancy. Subutex should only be used after obtaining and carefully documenting informed consent.

COCAINE ADDICTIONS

Cocaine is a local anesthetic and a potent, short-acting stimulant of the central nervous system. Illicit cocaine use is by inhalation of powder or intravenous injection. Other derivatives of cocaine, such as its pelleted free base ("crack"), are smoked, sometimes after mixing with tobacco or marijuana.

Whether cocaine causes human malformations is controversial. Several studies of the offspring of women who abused cocaine during pregnancy have described an increased incidence of cranial defects, including exencephaly, encephalocele, and parietal bone defects, limb reduction defects, urogenital abnormalities, and intestinal perforation, obstruc-

tion, or atresia.[129–131] Other studies have found no association between antenatal cocaine use and fetal malformations. Neerhof and colleagues[132] failed to find a significant increase in anomalies among 138 children born to women with positive screens for cocaine at the time of labor. Cocaine use in this report was, however, associated with an increase in preterm birth, intrauterine growth retardation, and placental abruption. The mechanism by which cocaine may induce placental abruption is via intense transient hypertension and vasoconstriction produced by the drug. Extensive study of the hemodynamic effects of cocaine on the pregnant ewe and fetus have confirmed this hypertensive response as well as a corresponding decrease in uterine blood flow that lasts approximately 15 minutes after initial administration.[133]

Topiramate, an anticonvulsant, raises cerebral GABA levels, facilitates GABAergic neurotransmission, and inhibits glutamatergic activity at AMPA/kainite receptors.[134] Because both GABAergic and glutamatergic neurons seem to be important modulators of the brain reward system, one may anticipate that Topiramate would be beneficial in treating cocaine addiction. Kampman and colleagues recently performed a pilot study of Topiramate in cocaine-addicted subjects.[135] In a double-blind, placebo-controlled trial of 40 such subjects during 13 weeks, they showed that after week 8, when the dose titration was completed, topiramate-treated subjects were more likely to be abstinent from cocaine compared with placebo-treated subjects. Topiramate-treated subjects also were more likely to attain 3 weeks of continuous abstinence from cocaine.

Currently, there are no studies on the potential benefits of topiramate for cocaine addiction during pregnancy; however, this medication is commonly used in pregnancy for treatment of seizure disorders. In the few cases in which fetal malformations are reported,[136,137] the constellation of malformations (growth deficiency, a third fontanelle, short nose with anteverted nares, blunt distal phalanges, and generalized blunting of the nails with fifth nail hypoplasia) is consistent with anomalies found in infants exposed prenatally to other anticonvulsants as well. Topiramate use during pregnancy for cocaine addiction may be justified, depending on the severity of the addiction and the physician's assessment of the risk to the fetus from ongoing cocaine use.

Baclofen is a GABA B receptor agonist that has drawn recent interest in the treatment of cocaine addiction. Several studies in laboratory animals have demonstrated attenuation of cocaine-seeking and a decrease in the selective molecular and behavioral effects of cocaine.[138,139] In a recent placebo-controlled, randomized trial of Baclofen,[140] 70 subjects were randomly assigned to Baclofen (20 mg t.i.d.) or placebo during a 16-week period. Primary outcome measures were retention in treatment, cocaine use, cocaine craving, and adverse events. Participants assigned to receive Baclofen demonstrated significant and stepwise increases in the probability of providing negative urine toxicology screens for benzoylecgonine. Participants assigned to placebo demonstrated no such association. There was no statistical significance observed for retention in treatment, cocaine craving, or incidence of reported adverse events. Baclofen is a muscle relaxant and antispasmodic and has been used in pregnancy for the treatment of spasticity in patients with pregnancies complicated by multiple sclerosis or spinal cord disease. The most common use during pregnancy is in spinal cord injury patients. Baclofen is effective, given via an intrathecal catheter, in preventing the enormous spastic symptoms and secondary autonomic dysregulation induced by uterine contractions.[141] Intrathecal delivery of the drug requires only approximately 1% of the dose necessary for oral administration. Placental transfer is sufficient enough that, when taken orally throughout pregnancy, a neonatal abstinence syndrome is observed, manifest largely by neonatal seizures.[142]

Assuming equal efficacy in the management of cocaine addiction, topiramate seems to be the safer of the 2 agents with respect to fetal effects. At this time, however, there is insufficient data to support the widespread use of either agent in the nonpregnant population. Further confirmatory studies are necessary to justify adoption into routine clinical practice. Use in pregnancy should be considered experimental and limited to use on protocol with well-documented informed consent. Given the promising preliminary reports of the therapeutic effects of both agents, optimism with respect to their future use seems justified.

METHAMPHETAMINE ADDICTIONS

Amphetamines are centrally acting stimulants that may have some efficacy in the treatment of narcolepsy but that are largely ineffective in the treatment of obesity. Methylphenidate has largely replaced methamphetamine in the management of narcolepsy during pregnancy. The abuse of methamphetamine leads to the ingestion of large and uncontrolled doses during pregnancy. When methamphetamine use has been studied among addicted mothers, the specific adverse effects of the drug is difficult to discern because of the confounding effects of other drugs used in combination (eg, ethanol) as well as poor maternal nutrition, hygiene, and attendance at prenatal visits.[143–145] Like cocaine, the preponderance of available data would suggest little or no effect of amphetamines on organogenesis. A recent, prospective evaluation of 228 amphetamine-exposed pregnancies by Jones and colleagues[146] did not show any increase in spontaneous abortion, major, or minor malformations. The effects of amphetamines on the gravid uterus and fetus are similar to those seen with cocaine. Stek and colleagues[147] have developed a model in pregnant ewes. Placental transfer of the drug is rapid and because the fetus has a longer elimination half-life than the mother, total exposure of the fetus is high. Maternal ingestion is associated with an elevation in both maternal and fetal blood pressure, and a decrease in fetal oxyhemoglobin saturation and pH. A transient increase in umbilical vascular resistance and a decrease in uterine blood flow accompanied these changes.[147,148]

At least 2 medications have been tested for the treatment of amphetamine addiction. Galloway and colleagues[149] conducted a randomized, clinical trial of imipramine in the treatment of methamphetamine dependence. Thirty-two patients were randomized to receive 10 or 150 mg of imipramine per day for 180 days. Retention in treatment was significantly

longer for subjects who were treated with 150 mg of imipramine compared with control. There was, however, no difference noted between the 2 groups of subjects in stimulant craving, self-report of time since last use of stimulants, or percent of urinalyses positive for stimulants. Vigabatrin (gamma vinyl-GABA), an irreversible inhibitor of GABA aminotransferase, also has been tested in patients with amphetamine dependence.[150] In that study, 16 of 18 patients tested negative for methamphetamine and cocaine during the last 6 weeks of the trial. GVG did not produce any visual field defects or alterations in visual acuity. Furthermore, it did not produce changes in vital signs even with continued use of methamphetamine and cocaine. Experience with Vigabatrin during pregnancy is limited, consisting only of case reports. There is insufficient data to comment on its safety.

In summary, pregnant women with addiction disorders represent both a unique challenge and an opportunity for the health care provider. Although not as prevalent as in men, women with substance abuse disorders differ significantly from men in patterns of use, agents they abuse, family history and predisposing factors. The observed co-occurring psychiatric disorders also differ from those of men. The added shame and guilt associated with the presence of the fetus will frequently add to break down the denial and allow opportunity for more effective intervention. Medical and obstetric complications from substance abuse and parallel high-risk behaviors represent a significant contribution to perinatal morbidity and mortality and can be reduced with aggressive screening and intervention. Currently, obstetric care providers in general lack sufficient skill to identify the addicted pregnant woman and refer for treatment. A goal of the addiction medicine community should be to provide this education where appropriate.

New and highly efficacious medications are becoming available at a pace never seen before in the field. The availability of Buprenorphine has moved opiate addiction from the methadone clinic to the physician's office. This has gone a long way to destigmatize the disease and has increased access to treatment to many who would not have otherwise had the opportunity. GABA-modulating agents show great promise as effective adjuncts to treatment of alcohol and cocaine addictions. With the exception of the currently ongoing Agonist Treatment of Opioid-Addicted Pregnant Women trial, few of the new agents have been tested in the gravid population. Clearly, more studies specifically directed at this special population are needed. This does not necessarily exclude pregnant women from access to treatment because, as with most other medications, off-label prescribing may still be appropriate provided certain criteria apply. Proper communication between the obstetric care provider and the addiction treatment team will ensure that medications will be selected to provide the best potential efficacy while minimizing risk to the fetus. In addition to identification of medications that might be reasonably safe and effective in maintaining abstinence, these lines of communication will provide for the development of more rational antepartum testing schedules designed to meet the needs of the individual patient. As with many other complex medical problems that occur during pregnancy, addiction treatment during pregnancy can be improved greatly with a cooperative team approach.

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