LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their thrice-weekly rounds, Dr. Stern and other members of the Psychiatric Consultation Service discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Cocaine and Opioid Use During Pregnancy: Prevalence and Management

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Have you ever wondered which of your patients may be using cocaine or opioids during pregnancy and concealing this use for fear of stigma? Have you deliberated about how to best educate the substance-using woman who presents to your practice without prenatal care? Have you been concerned about the risk of human immunodeficiency virus (HIV), hepatitis, endocarditis, or other complications from intravenous (IV) drug use in pregnancy? Have you wondered how to inform women about the risks of neonatal withdrawal from opioids and the need for maintenance during pregnancy and the postpartum period?

If you have, then the following discussion should serve as a stimulus for the management of the psychiatric aspects of cocaine and opioid use during pregnancy and the postpartum management of the mother and the neonate.

What Is the Epidemiology of Cocaine Use During Pregnancy?

In the United States alone, there are an estimated 2.4 million frequent (i.e., at least twice weekly) users of cocaine, according to the 2005 National Survey on Drug Use and Health (NSDUH).[1] Extrapolating from data from the NSDUH, the Drug Use Forecasting program (which measures active use among arrestees for drug-related charges), and the National Institute of Justice, the White House Drug Policy Epidemiology Program estimates that up to $70 billion was spent on cocaine each year between 1990 and 1999 and that, in addition to regular users, there are up to 4.6 million occasional users of cocaine (i.e., once a month or less), excluding individuals already in prison.[2]

It is difficult to determine how many pregnant women use cocaine nationwide. The 2005 NSDUH estimates that there is approximately a 4% prevalence of illicit drug use among pregnant women, compared with a 10% rate of illicit drug use among nonpregnant, reproductive-aged women (aged 15–44 years).[1] This 2005 estimate of the prevalence of drug use in pregnancy represents an increase from the 1994 finding of a 2.3% prevalence of any illicit drug use among pregnant women in this age group.[3]

Although the rates of alkaloidal (crack) cocaine use appear to have been declining since the mid-1980s (after being the subject of much media and scholarly attention around that time), 1 study using meconium analysis in a Detroit cohort of 3000 women found a 31% prevalence of cocaine use close to delivery (despite only 11% of the women reporting any drug use)[4]; this finding was corroborated by other studies.[5,6] In line with declining rates of use, the 1992 National Institute on Drug Abuse National Pregnancy and Health Survey (which was not repeated annually) estimated the rate of cocaine use during pregnancy as 1.1% (of women under age 44 years who had used cocaine at any point in pregnancy).[7]

However, data within the last decade from the NSDUH found that, of the 2.8% of women who used illicit drugs during pregnancy in the 1996–1998 survey, 75% used marijuana, while 10% used cocaine.[8] Thus, as a proportion

of illicit drug use among pregnant women, cocaine is still significant. The NSDUH further described a pattern of illicit drug use in pregnancy by trimester: in the 1 month preceding the 1999 and 2000 studies, there was a 4% rate of use among women in their first trimester, 3% among those in their second trimester, and 2% among those in their third trimester, with the decline attributed to response to pregnancy.[9] While most pregnant women who use cocaine and other illicit drugs are not involved in drug trafficking, the economic burden on both recreational and dependent users is influenced by drug enforcement and drug-related crimes, with 1 study finding that a mere $10 increase in the price per gram of cocaine decreased demand among pregnant women by 12% to 15%.[10] In addition, other psychosocial difficulties that may be associated with illicit drug use include lack of stable housing, lack of vocational and educational resources, and increased risk of interpersonal violence, including accidental and drug-related homicide.[11]

How Should Women Be Screened for Cocaine and Opioid Use in Pregnancy?

In contrast to screening for alcohol in pregnancy, for which the T-ACE (Tolerance, Annoyed, Cut-down, Eye-opener) has been demonstrated as particularly effective, there are no specific verbal screening instruments for illicit substance use in pregnancy. Neither the Drug Abuse Screening Test (DAST), nor the CAGE-AID (Cut-down, Annoyed, Guilt, Eye-opener; the CAGE version adapted to include drug and alcohol use) have been tested among pregnant women. In the absence of a validated formal screening instrument, nonjudgmental, open-ended questions about prepregnancy substance use (both at early evaluations and at follow-up to positive screens) may be useful.[12] Of note, most cocaine use in particular (and much illicit drug use in general) by pregnant women is recreational and occasional, rather than representing addiction.[3] Therefore, screening should target "any use," rather than simply DSM criteria for abuse or dependence.

The preferred biological method of screening for cocaine use in pregnancy involves use of urine toxicology, which typically detects the metabolite benzoylecgonine up to 72 hours after use. Some authors have noted that metabolites may show up in urine as long as 2 weeks after use, depending on the screening sensitivity.[13] Serum toxicology, done routinely at prenatal visits, should include drugs of abuse, if possible, since benzoylecgonine will also show up in a serum toxicology screen up to 8 hours after cocaine use.[13]

Confirmation of opioid use during pregnancy also relies on urine toxicology screening; after findings on the physical examination (such as track marks) or patient self-report, urine screening is efficient and is often the most rapid tool available. Methadone may be detected in the urine up to 2 weeks after use, although a specific "drugs of abuse" urine toxicology screen may be required that is not available at all facilities. Heroin remains detectable in the urine for up to 72 hours after use. Fentanyl, like methadone, may not be revealed in conventional urine toxicology screens and may require a specific screening request, though its metabolite, norfentanyl, may be detected for a longer period of time.[14] Neonatal meconium, while shown to have equivalent or greater sensitivity for maternal opioid use compared with urine toxicology, is not yet widely available. For screening in the office, the DAST is widely used, although no single screening questionnaire for opioid use has been established as being better than any other.[15]

Though the legal implications of substance use in pregnancy vary by state and go beyond the scope of this article, it should be mentioned that several states have adopted mandatory drug screening of women who present for delivery. While efforts have been more focused on inpatient screening in labor wards (rather than at prenatal visits), wide latitude exists for physicians to initiate screening based on clinical suspicion, verbal admission of any substance use, or positive tests for HIV, hepatitis A or B, or other sexually transmitted diseases for which IV drug use may also be a risk factor.[16] Widespread testing in urban hospitals and of minority and low socioeconomic status women in particular (initiated in the early 1990s) has more recently led to concerns about the possible coordination of physician testing with drug enforcement being targeted specifically at poor women. In some states, a positive test at presentation for delivery initiates an arrest and not only incarceration, but also possibly homicide charges if drug use is causally linked with fetal demise. Most health care providers, however, have argued for following positive testing with drug counseling, confidential screening in the context of a patient-physician relationship, and referral for treatment and case management rather than criminal penalties.[17]

How Does Cocaine Affect the Normal Physiology of Pregnancy, and How Should These Complications Be Managed?

Placental abruption (caused by vasospasm and hypoxia to the placental bed) is commonly cited as an adverse effect of cocaine use during pregnancy, although this may be more associated with cocaine bingeing than with sporadic use.[18] Also seen are premature rupture of membranes, preterm labor, preterm delivery, and maternal seizures. Uterine contractions are commonly caused by cocaine (perhaps due to β-agonist action on the β_2 receptors of the uterus).[12]

Complications of cocaine, including abruption, that can be assessed by ultrasound should be considered at 32 weeks of gestation but before this should be considered in

the planning of prenatal follow-ups.[12] In addition to timed screenings, serial ultrasounds on a monthly basis are used to assess fetal growth and well-being, as well as to look at placental integrity. Serial ultrasounds are also used in surveillance for adverse effects of other drugs of abuse in pregnancy.[19] In addition to prenatal monitoring, caring for the substance-affected woman should also involve repeat sexually transmitted disease (STD) screening at the initial visit and at week 36, as well as appropriate treatment.[20]

Other maternal complications may result from poor medical and prenatal care compliance that is in part physiologically, rather than psychologically, mediated. Following cocaine use, there is a 2-hour high (with the peak of the high reached within the first hour) and then a characteristic "crash" with irritability, discomfort, and depression (from catecholamine depletion at the synapse). This state leads to craving of the next "dose," which becomes the physiologic priority for the dependent user.[13] This phenomenon is particularly pronounced with crack cocaine, which delivers in 1 dose at least 10 times the amount of cocaine present in 1 "line" (250–1000 mg in 1 "hit" vs. 25 mg in a line of cocaine).[21]

Migraine headaches, which become more prevalent during pregnancy (likely due to increased production of estrogen), are also more common among cocaine users, further contributing to the picture of irritability.[12] Both hemorrhagic and ischemic cerebrovascular accidents may occur. Dyspnea during pregnancy, which is due to a decreased tidal volume from the compression of the lower lung fields by the expanding uterus, may be indicative of "crack lung" or pneumonitis in a cocaine user—characterized by fevers, pulmonary infiltrates, and leukocytosis; it is treated with oral steroids but can be severe enough to cause acute respiratory failure and make patients ventilator dependent.[22,23] Hyperthermia mediated by vasoconstriction and/or the hypermetabolic state of cocaine use may also be observed, and this should be considered during pregnancy as an effect that might counteract the expected physiologic vasodilation (and normal lowering of blood pressure seen in pregnancy) from increased levels of progesterone. Hyperthermia from multiple causes (including pyelonephritis and other infections) has been linked with prematurity, low birth weight, and (rarely) fetal death.[24] Cocaine-induced hyperthermia may also cause an altered mental status in the mother, including an excited delirium (in addition to other cocaine-induced states of delirium from cardiac or respiratory failure, stroke, the intoxication syndrome, or infectious sequelae of use) and should be on the list of causes of delirium in a pregnant woman and managed aggressively.[25]

In addition to jeopardizing the fetal-placental circulation, cocaine may cause longer-term complications for the fetus, the neonate, and the developing child. There is an increased risk of infection with HIV and other infectious agents via vertical transmission from mother to fetus due to cocaine-induced vasculopathy.[26] Finally, this same vasculopathy reduces the efficacy of the fetal blood-brain barrier, in turn facilitating fetal exposure to other teratogenic substances—a clinically significant problem since cocaine is rarely used alone by those with addictions.[12] What are less clear are the nature and extent of developmental changes caused by prenatal exposure to cocaine; some studies have suggested that subtle cognitive and behavioral impairments occur from the neonatal stage to adolescence,[27,28] but the multiple exposures of polysubstance use (including well-studied teratogens like alcohol) represent confounding variables. In addition to other substances used separately at different points in pregnancy, some use of complementary substances, such as alcohol or benzodiazepines to mediate the "crash" following cocaine-induced intoxication, may further amplify risks. In addition to benzodiazepines used alone as a cause of cleft palate,[29] animal studies have shown that benzodiazepines in combination with cocaine increase the incidence of malformations (such as hydronephrosis, cryptorchidism, and incomplete ossification of the skeleton).[30]

Immediately before delivery, as well as during delivery and the postpartum period, management of the substance-using mother is with supportive care. Additional monitoring with telemetry and arterial blood gases is usually reserved for those pregnancies classified as "high risk" for reasons other than cocaine use alone.

Although the syndrome of cocaine withdrawal is not life threatening for the mother or for the fetus, the mood symptoms (and potential effect on noncompliance) have been ameliorated with use of short-acting benzodiazepines for the mother, particularly during inpatient stays.[31] Less commonly, hallucinations may occur during withdrawal (though psychosis is more often seen as part of the intoxication syndrome called toxic paranoid psychosis) and if present may require use of antipsychotics.[21]

Other regimens have included prophylactic treatment (with selective serotonin reuptake inhibitors [SSRIs], bupropion, methylphenidate, and tricyclic antidepressants [TCAs]) for depression and irritability.[32,33] Standard care does not currently include the use of anticraving medications, though several agents that are already U.S. Food and Drug Administration (FDA)–approved for other uses (e.g., disulfiram, modafinil, propranolol, topiramate, and vigabatrin) have also been shown to reduce cocaine cravings.[34]

Of these, none are absolutely contraindicated in pregnancy, and all are designated as category C; some animal data show teratogenicity, and the risks and benefits must be weighed for each individual pregnant woman before treatment.

What Is the Epidemiology of Opioid Use During Pregnancy, and How Do Opioid-Related Problems Present?

Among the opioids, heroin and methadone are the most commonly used forms by pregnant women.[1] Over the past decade, heroin (smoked recreationally, rather than injected, in formulations that are 1% to 98% pure, with quinine, starch, or sugar often used as elements in the mixture) use has been on the increase. It is estimated that approximately 7000 opiate-exposed births occur annually.[35] While obstetrical complications associated with opioid use in pregnancy vary greatly, there has been up to a 6-fold increase in obstetrical complications associated with this phenomenon.[36]

Overdose of opioids in pregnancy is manifest by the same signs and symptoms (e.g., coma, circulatory collapse, pinpoint pupils, bradycardia, hypothermia, and severe respiratory depression) as opioid overdose in the nonpregnant women.[37]

Opioid withdrawal may be difficult to distinguish from other more commonly observed syndromes, such as upper respiratory infections. Opioids have a rapid transplacental passage (less than 60 minutes), and maternal and fetal withdrawal is likely to begin 6 to 48 hours after last usage.[38] The maternal opioid withdrawal syndrome is characterized by influenza-like symptoms (e.g., myalgias) and signs (e.g., rhinorrhea and lacrimation), as well as by anorexia that can result in impaired fetal growth. The stress state that characterizes withdrawal may also have a negative impact on the fetus; some studies show increased epinephrine in amniotic fluid.[39]

Neonatal abstinence syndrome from opioids has been well-characterized and may last up to 10 weeks following delivery and require management in an intensive care unit. Neonatal abstinence syndrome involves wakefulness, irritability, tremulousness, and temperature dysregulation, as well as a disorganized suck and subsequent failure to thrive. Seizures have also been reported.[40,41] While higher doses of methadone or other opiates during pregnancy are associated with more severe manifestations of neonatal abstinence syndrome in the neonate, withdrawal during pregnancy is associated with worse outcomes for the fetus overall. Although the mechanism of fetal death in connection with withdrawal is uncertain, it may involve hyperactivity secondary to premature contractions, hypoxia, or possibly meconium aspiration. Therefore, it is the current standard of care to maintain opioid-dependent women on long-acting narcotics during pregnancy rather than initiate any type of withdrawal protocol.[35,40]

What Are the Clinical Options for Managing Opioid Use During Pregnancy?

Several clinical options for management of prenatal opiate use are available. The first is methadone maintenance; this has been the standard of care since the early 1970s. The second involves use of buprenorphine and naltrexone; they appear equally safe, although this is not yet established. The third (via limited clinical trials) is opioid detoxification (particularly during the second trimester).[36]

The metabolism of methadone is increased in pregnancy (via the effect of increased progesterone on liver cytochrome P450 enzymes).[42] Clinically, this effect has led to the recommendation that, should pregnant women report withdrawal symptoms on their maintenance dose, this report should be taken seriously and the dose adjusted according to their current withdrawal signs and symptoms. In addition to the decreased plasma protein binding of methadone, increased metabolism has resulted in a shortened half-life of methadone during the third trimester in particular (somewhat less than the standard 24- to 36-hour half-life of the drug).[42] To begin the maintenance regimen, patients already on outpatient methadone maintenance should be continued on their outpatient dose (after it has been verified, preferably via a written record, with their outpatient provider or licensed clinic).[43] Heroin and fentanyl users should be converted to using methadone during pregnancy so that there will be fewer withdrawal cycles. Conversion is associated with fewer spontaneous abortions as well as a reduced risk of intravenously transmitted infections.[43] It has been estimated that there is a rate of 3% to 4% of spontaneous abortion with methadone (and possibly with buprenorphine maintenance)[44,45] compared with a rate of 10% to 20% in women who continue to use heroin; this higher rate is attributed to wide variations in level of opiates and resulting fetal stress.[46] In making the conversion to methadone, the starting dose often ranges from 1 to 20 mg; patients are then dosed on an as-needed basis for signs and symptoms of opiate withdrawal (including subjective cravings) every 6 hours, with most patients reaching a stable dose after 48 to 72 hours.[45]

Cultural and psychological barriers among this population to using methadone should be addressed. Women in early recovery may be resistant to being "on drugs" again. Incarcerated pregnant women may have difficulties gaining access to the medication or be the target of disapproval from prison authorities for receiving it under federal mandate that makes methadone maintenance an entitlement for all pregnant women.[47] Some patients believe that methadone is categorically "bad for the heart" and should be avoided at all costs. In recent case reports, methadone has indeed been correlated with cardiac side effects, among them torsades de pointes and ventricular arrhythmias.[48] Therefore, a discussion of taboos against methadone should be balanced with a fact-based discussion of benefits of avoiding withdrawal in pregnancy versus the risk of methadone-induced arrhythmias among pregnant women and possible induction of fetal arrhythmias by methadone exposure.[49,50]

Some debate exists as to whether specialized multiservice programs for pregnant women, versus receiving methadone from an outpatient methadone clinic, carry greater physiologic, psychosocial, and medical benefits for this population. An early study by Chang and colleagues[51] showed that enhanced prenatal care and comprehensive services have better results than a traditional methadone program despite equivalent dose ranges for maintenance.[51,52] There is also some debate about whether higher or lower doses at delivery are of particular benefit. Lower doses are associated with less neonatal withdrawal, but higher doses during the pregnancy and at delivery are associated with better patient compliance, reduced relapse risk, and higher neonatal birthweights.[43] Split-dosing trials of methadone have also been associated with preliminary favorable results and may also reduce concomitant cocaine cravings in these women.[53] Perhaps the only finding that may argue for a highly selective inclusion of pregnant women in methadone maintenance is that increased neonatal mortality has been associated with women who relapse to heroin while taking methadone, as compared with women using heroin alone.[45]

Buprenorphine as an alternative to methadone in pregnancy has been validated by several naturalistic studies in France, where outpatient physicians can treat with buprenorphine without specialized training; up to 70,000 patients annually have received the medication on an outpatient basis since the 1996 liberalization of policies.[54] Though several French and some American studies report positive findings for buprenorphine in pregnancy,[55,56] greater severity of the neonatal abstinence syndrome and higher rates of sudden infant death were described in 1 Finnish study.[57]

Naltrexone may also play a role in relapse prevention, and it has been used for maintenance after an initial taper with buprenorphine. In 1 small Australian study, naltrexone was used for a detoxification protocol during pregnancy with favorable results.[58] The pilot results of a naltrexone implant for this purpose have also been promising.[59]

Opioid detoxification is typically avoided in the first trimester due to an association of spontaneous abortion with withdrawal.[40] It is also avoided during the third trimester due to the association with fetal stress and preterm labor. In a carefully controlled second trimester detoxification regimen restricted to inpatient perinatal units, the outpatient methadone dose was decreased by about 1 mg per day in some studies, with a dose reduction in outpatient settings of 5 mg every 2 weeks (though neither of these numbers should be used as clinical guidelines, as these doses were generalized from relatively small study populations).[35]

The indications for opioid detoxification during pregnancy include the absence of methadone maintenance where the patient lives, as well as a patient's strong wish for detoxification (and likely determination to "self-detox" if she is not offered any medical management). It should be again emphasized that detoxification during pregnancy at the current time does not represent the standard of care. But, access to standard treatment cannot be taken for granted; out of 13,000 substance abuse treatment facilities responding in the 2005 NSDUH, only 8% operate a certified Opioid Treatment Program certified by the Substance Abuse and Mental Health Services Agency of the National Institutes of Health, and perhaps only one half of these serve pregnant women.[1]

What Are the Psychological Aspects of Substance Use During Pregnancy?

The image of drug-dependent pregnant women determined to stop using drugs for their baby's sake is a compelling one, and it arguably fulfills the social expectation of motherhood as sacrifice and as an encompassing, altruistic identity. While pregnancy may indeed act as a motive for women to seek treatment for substance abuse, studies on maternal-fetal attachment in these populations have shown a range of emotions regarding pregnancy.[60] An unwanted pregnancy or one that has occurred as the result of sexual coercion (either from a violent partner or during prostitution for drugs) may not have any impact on use. Women may be desensitized to the consequences of continuing to use illicit drugs during pregnancy by the loss of their previous children to social services or to other agencies, which are aimed at child protection but often achieve this at the expense of maternal-child bonding.[61] Parenting stress has been shown to be a common trigger for substance relapse, even in women who are medically managed during pregnancy[62]; thus, parenting support groups are as important as court-mandated drug treatment for postdelivery mothers. Postnatal attachment has also been identified as a point of intervention, with the postnatal environment on some analyses seen as a greater determinant of developmental progress in children than their prenatal exposure to heroin.[63]

Given that pregnancy may not elicit feelings of safety or well-being, a sense of purpose, or a resolution on the part of addicted pregnant women to achieve healthy survival for themselves and their children, the possibility of suicide must be carefully considered in this population and screened for at prenatal visits, along with depression and other common psychiatric disorders. Although rates of suicide attempts are about one third lower among pregnant women than among nonpregnant women, in 1 cohort of pregnant substance abusers, a 13% rate of suicide was detected.[64] In comparison to more recent studies, both in the United States and abroad, this rate may be disproportionately high, with 1 large cohort of pregnant women in public health clinics showing only a 0.38% prevalence of

suicidal poisonings during pregnancy between 2001 and 2004.[65] However, associated mood disorders affect the efficacy of substance treatment in pregnancy and are correlated with increased suicidal ideation that may increase the risk of postpartum events, including maternal suicide and infanticide.[66] In the U.S. study, there was an additional 1% maternal death rate associated with suicidal gestures that were not intended to be lethal (either to the mother or to the fetus).[64] The differential diagnosis of overdose in pregnancy includes suicidal gestures, attempts to induce abortions (as by quinine overdoses), accidental overdoses (most commonly with heroin), and frank suicide attempt with lethal intentions.[64]

What Other Clinical or Policy Questions Should Guide Services for Pregnant Substance Users?

As mentioned above, a full discussion of the medicolegal aspects of managing substance abuse in pregnancy is beyond the scope of this article, though a reference to a database on this topic is included here.[67] To date, the prosecution of pregnant substance abusers has been weighted toward illicit drug use rather than alcohol use, though alcohol is much more commonly used than all illicit drugs (apart from marijuana) in pregnancy.[1] No state has a law specifically criminalizing substance abuse in pregnancy, but approximately 30 states have prosecuted pregnant substance users through a state-by-state interpretation of "reckless endangerment" and "giving drugs to a minor" laws.[68] In at least 1 state, studies of reporting patterns showed that indigent women were more likely to be reported, though this did not correlate with greater access or referral to treatment.[69] Reporting guidelines are unclear and do not fall neatly under the mandatory reporter guidelines that exist for the physical, sexual, or verbal abuse of children, the elderly, and the handicapped. However, the standard of care for reporting currently includes (at a minimum) the involvement of social work services at any facility that manages the pregnancy as well as a report to the local child protective services agency (to plan for care of the infant after delivery and, where possible, to provide a timeline whereby the mother may regain custodial rights by going through a course of drug treatment and rehabilitation if she is motivated).[68]

Even for motivated women, obtaining treatment is not always straightforward. The scarcity of specialized treatment centers has already been noted. The relative scarcity of obstetrician-gynecologists who specialize in high-risk pregnancies also makes it challenging to find longitudinal services from prenatal care to the postpartum period.[70] Relatively few facilities will accept women with children for residential treatment, though this is often what is required for the well-being of the family. There continue to be service and research needs for addiction treatment and obstetrics, with collaborations offering the greatest potential for meeting unmet needs and interconception care and counseling a priority for preventing substance-exposed pregnancies.

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