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This information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Opioid Abuse, Dependence, and Addiction in Pregnancy

ABSTRACT: Opioid use in pregnancy is not uncommon, and the use of illicit opioids during pregnancy is associated with an increased risk of adverse outcomes. The current standard of care for pregnant women with opioid dependence is referral for opioid-assisted therapy with methadone, but emerging evidence suggests that buprenorphine also should be considered. Medically supervised tapered doses of opioids during pregnancy often result in relapse to former use. Abrupt discontinuation of opioids in an opioid-dependent pregnant woman can result in preterm labor, fetal distress, or fetal demise. During the intrapartum and postpartum period, special considerations are needed for women who are opioid dependent to ensure appropriate pain management, to prevent postpartum relapse and a risk of overdose, and to ensure adequate contraception to prevent unintended pregnancies. Patient stabilization with opioid-assisted therapy is compatible with breastfeeding. Neonatal abstinence syndrome is an expected and treatable condition that follows prenatal exposure to opioid agonists.

Opioid abuse in pregnancy includes the use of heroin and the misuse of prescription opioid analgesic medications. According to the 2010 National Survey on Drug Use and Health, an estimated 4.4% of pregnant women reported illicit drug use in the past 30 days (1). A second study showed that whereas 0.1% of pregnant women were estimated to have used heroin in the past 30 days, 1% of pregnant women reported nonmedical use of opioid-containing pain medication (2). In this study, the rates of use varied by setting and by mode of assessment. The urine screening of pregnant women in an urban teaching hospital resulted in a detection rate for opioids of 2.6% (2). The prevalence of opioid abuse during pregnancy requires that practicing obstetrician–gynecologists be aware of the implications of opioid abuse by pregnant women and of appropriate management strategies.

Pharmacology and Physiology of Opioid Addiction

Opioid addiction may develop with repetitive use of either prescription opioid analgesics or heroin. Heroin is the most rapidly acting of the opioids and is highly addictive (3). Heroin may be injected, smoked, or nasally inhaled. Heroin has a short half-life, and a heroin user may need to take multiple doses daily to maintain the drug's effects. Prescribed opioids that may be abused include codeine, fentanyl, morphine, opium, methadone, oxycodone, meperidine, hydromorphone, hydrocodone, propoxyphene, and buprenorphine (the partial agonist). These products may variously be swallowed, injected, nasally inhaled, smoked, chewed, or used as suppositories (4). The onset and intensity of euphoria will vary based on how the drug was taken and the formulation; however, all have the potential for overdose, physical dependence, abuse, and addiction. Injection of opioids also carries the risk of cellulitis and abscess formation at the injection site, sepsis, endocarditis, osteomyelitis, hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infection.

Opioids bind to opioid receptors in the brain and produce a pleasurable sensation (3). Opioids also depress respiration, potentially resulting in respiratory arrest and death. Opioid addiction is associated with compulsive drug-seeking behavior, physical dependence, and tolerance that lead to the need for ever higher doses (4). Once physical dependence to an opioid has developed, a withdrawal syndrome occurs if use is discontinued. With short-acting opioids, such as heroin, withdrawal symptoms may develop within 4–6 hours of use, may progress up to 72 hours, and usually subside within a week. For long-acting opioids, such as methadone, withdrawal

symptoms are usually experienced between 24 hours and 36 hours of use and may last for several weeks. Obsessive thinking and drug cravings may persist for years, thus leading to relapse. Although heroin withdrawal is not fatal to healthy adults, fetal death is a risk in pregnant women who are not treated for opioid addiction because their offspring experience acute opioid abstinence syndrome (5).

Effects on Pregnancy and Pregnancy Outcome

An association between first-trimester use of codeine and congenital heart defects has been found in three of four case–control studies (6–9). Previous reports have not shown an increase in risks of birth defects after prenatal exposure to oxycodone, propoxyphene, or meperidine (10, 11). The authors of one retrospective study observed an increased risk of some birth defects with the use of prescribed opioids by women in the month before or during the first trimester of pregnancy (12). However, methodological problems with this study exist, and such an association has not been previously reported. The observed birth defects remain rare with a minute increase in absolute risk. Although none of these studies investigated methadone or buprenorphine specifically, concern about a potential small increased risk of birth defects associated with opioid-assisted therapy during pregnancy must be weighed against the clear risks associated with the ongoing use of illicit opioids by a pregnant woman.

During pregnancy, chronic untreated heroin use is associated with an increased risk of fetal growth restriction, abruptio placentae, fetal death, preterm labor, and intrauterine passage of meconium (13). These effects may be related to the repeated exposure of the fetus to opioid withdrawal as well as the effects of withdrawal on placental function. Additionally, the lifestyle issues associated with illicit drug use put the pregnant woman at risk of engaging in activities, such as prostitution, theft, and violence, to support herself or her addiction. Such activities expose women to sexually transmitted infections, becoming victims of violence, and legal consequences, including loss of child custody, criminal proceedings, or incarceration.

Screening for Opioid Use, Abuse, and Addiction

Screening for substance abuse is a part of complete obstetric care and should be done in partnership with the pregnant woman. Both before pregnancy and in early pregnancy, all women should be routinely asked about their use of alcohol and drugs, including prescription opioids and other medications used for nonmedical reasons. To begin the conversation, the patient should be informed that these questions are asked of all pregnant women to ensure they receive the care they require for themselves and their fetuses and that the information will be kept confidential. Maintaining a caring and nonjudgmental approach is important and will yield the most inclusive disclosure. Routine screening should rely on validated screening tools, such as questionnaires including 4P's and CRAFFT (for women aged 26 years or younger) (Box 1) (14, 15).

In addition to the use of screening tools, certain signs and symptoms may suggest a substance use disorder in a

Box 1. Clinical Screening Tools for Prenatal Substance Use and Abuse ⇦

4 P's

Parents: Did any of your parents have a problem with alcohol or other drug use?

Partner: Does your partner have a problem with alcohol or drug use?

Past: In the past, have you had difficulties in your life because of alcohol or other drugs, including prescription medications?

Present: In the past month have you drunk any alcohol or used other drugs?

Scoring: Any "yes" should trigger further questions.

Ewing H. A practical guide to intervention in health and social services with pregnant and postpartum addicts and alcoholics: theoretical framework, brief screening tool, key interview questions, and strategies for referral to recovery resources. Martinez (CA): The Born Free Project, Contra Costa County Department of Health Services; 1990.

CRAFFT—Substance Abuse Screen for Adolescents and Young Adults

C Have you ever ridden in a CAR driven by someone (including yourself) who was high or had been using alcohol or drugs?

R Do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in?

A Do you ever use alcohol or drugs while you are by yourself or ALONE?

F Do you ever FORGET things you did while using alcohol or drugs?

F Do your FAMILY or friends ever tell you that you should cut down on your drinking or drug use?

T Have you ever gotten in TROUBLE while you were using alcohol or drugs?

Scoring: Two or more positive items indicate the need for further assessment.

Center for Adolescent Substance Abuse Research, Children's Hospital Boston. The CRAFFT screening interview. Boston (MA): CeASAR; 2009. Available at: http://www.ceasar.org/CRAFFT/pdf/CRAFFT_English.pdf. Retrieved February 10, 2012.

pregnant woman. Pregnant women with opioid addiction often seek prenatal care late in pregnancy; exhibit poor adherence to their appointments; experience poor weight gain; or exhibit sedation, intoxication, withdrawal, or erratic behavior. On physical examination, some signs of drug use may be present, such as track marks from intravenous injection, lesions from interdermal injections or "skin popping," abscesses, or cellulitis. Positive results of serologic tests for HIV, hepatitis B, or hepatitis C also may indicate substance abuse. Urine drug testing is an adjunct to detect or confirm suspected substance use, but should be performed only with the patient's consent and in compliance with state laws. Pregnant women must be informed of the potential ramifications of a positive test result, including any mandatory reporting requirements (16). Laboratory testing for HIV, hepatitis B, and hepatitis C should be repeated in the third trimester, if indicated (17).

The use of an antagonist, such as naloxone, to diagnose opioid dependence in pregnant women is contraindicated because induced withdrawal may precipitate preterm labor or fetal distress (13). Naloxone should be used only in the case of maternal overdose to save the woman's life.

Treatment

Since the 1970s, maintenance therapy with methadone has been the standard treatment of heroin addiction during pregnancy (13). Recently, this treatment also has been used for nonheroin opioid addiction (13) although the benefits are less well documented than for the treatment of heroin dependence.

The rationale for opioid-assisted therapy during pregnancy is to prevent complications of illicit opioid use and narcotic withdrawal, encourage prenatal care and drug treatment, reduce criminal activity, and avoid risks to the patient of associating with a drug culture. Comprehensive opioid-assisted therapy that includes prenatal care reduces the risk of obstetric complications (13). Neonatal abstinence syndrome is an expected and treatable condition that follows prenatal exposure to opioid agonists and requires collaboration with the pediatric care team. Methadone has significant pharmacokinetic interactions with many other drugs, including antiretroviral agents.

Methadone maintenance, as prescribed and dispensed on a daily basis by a registered substance abuse treatment program, is part of a comprehensive package of prenatal care, chemical dependency counseling, family therapy, nutritional education, and other medical and psychosocial services as indicated for pregnant women with opioid dependence. Perinatal methadone dosages are managed by addiction treatment specialists within registered methadone treatment programs. A list of local treatment programs for opioid addiction can be found at the Substance Abuse and Mental Health Services Administration's web site (http://dpt2.samhsa.gov/treatment/directory.aspx). Obstetricians should communicate with the addiction treatment program whenever there are concerns about the patient's care and methadone dosage. The dosage should be adjusted throughout the pregnancy to avoid withdrawal symptoms, which include drug cravings, abdominal cramps, nausea, insomnia, irritability, and anxiety. If a woman is treated with a stable methadone dosage before pregnancy, pharmacokinetic changes may require dosage adjustments, especially in the third trimester (18). Some women develop rapid metabolism to the extent that it becomes difficult to control withdrawal symptoms for 24 hours on a single daily dose; in these cases, split dosages may be optimal. Not all women require dose increases during pregnancy and any dosage adjustments should be made on clinical grounds by the addiction specialist. Methadone dosages usually are initiated at 10–30 mg/d (13). If a woman begins treatment with methadone while pregnant, her dosage should be titrated until she is asymptomatic in accordance with safe induction protocols. An inadequate maternal methadone dosage may result in mild to moderate opioid withdrawal signs and symptoms and cause fetal stress and increased likelihood for the maternal use of illicit drugs. Separate studies examined the extent to which the maternal methadone dosage is related to the severity of neonatal abstinence syndrome. The results are inconclusive and conflicting (19, 20). One systematic literature review and meta-analysis concluded that the severity of neonatal abstinence syndrome does not appear to differ based on the maternal dosage of methadone treatment (21). These maternal, fetal, and neonatal findings all underscore the need to provide pregnant women with an adequate methadone dosage that relieves and prevents opioid withdrawal signs and symptoms and also blocks the euphoric effect of misused opioids.

In most situations, it is advisable for pregnant women to initiate methadone induction in a licensed outpatient methadone program. In situations when a pregnant woman requires hospitalization for initiation of methadone treatment, an arrangement must be made before discharge for next day admission to an outpatient program. With the exception of buprenorphine, it is illegal for a physician to write a prescription for any other opioid for the treatment of opioid dependence, including methadone, outside of a licensed treatment program (22). Buprenorphine, when prescribed by accredited physicians who have undergone specific credentialing, is the only opioid approved for the treatment of opioid dependence in an office-based setting (23). Physicians should be familiar with federal and state regulations regarding prescribing of medications for the treatment of opioid dependence.

Emerging evidence supports the use of buprenorphine for opioid-assisted treatment during pregnancy. Buprenorphine acts on the same receptors as heroin and morphine (24). With appropriate informed consent, including disclosure of the lack of evidence from long-

term neurodevelopmental studies, buprenorphine also may be offered to patients in need of opioid-assisted therapy during pregnancy (25). The advantages of buprenorphine over methadone include a lower risk of overdose, fewer drug interactions, the ability to be treated on an outpatient basis without the need for daily visits to a licensed treatment program, and evidence of less severe neonatal abstinence syndrome (25). The disadvantages compared with methadone include reports of hepatic dysfunction, the lack of long-term data on infant and child effects, a clinically important patient dropout rate due to dissatisfaction with the drug, a more difficult induction with the potential risk of precipitated withdrawal, and an increased risk of diversion (ie, sharing or sale) of prescribed buprenorphine (25). Buprenorphine is available as a single-agent product or in a combined formulation with naloxone, an opioid antagonist used to reduce diversion. Buprenorphine with naloxone is formulated to prevent injected use because naloxone causes severe withdrawal symptoms when injected. However, because of poor naloxone absorption, the formulation has rare adverse effects when used sublingually as directed (24). The single-agent product is recommended during pregnancy to avoid any potential prenatal exposure to naloxone, especially if injected (25). The single-agent buprenorphine product has a higher potential to lead to abuse as well as a higher street value than the combination product. Thus, all patients should be monitored for the risk of diversion of their medication, especially if the single product is prescribed. Unlike methadone, which may be administered only through very tightly controlled programs, buprenorphine may be prescribed by trained and approved physicians in a medical office setting, which potentially increases the availability of treatment and decreases the stigma (24). The Substance Abuse and Mental Health Services Administration publishes a directory of physicians licensed to dispense buprenorphine (http://buprenorphine.samhsa.gov/bwns_locator). Patients considered for using buprenorphine need to be able to self-administer the drug safely and maintain adherence with their treatment regimen. Compared with methadone clinics, the less stringent structure of buprenorphine treatment may make it inappropriate for some patients who require more intensive structure and supervision (17).

Until recently, data on use of buprenorphine in pregnancy were relatively limited (25). A 2010 multicenter, randomized clinical trial compared the neonatal effects of buprenorphine and methadone in 175 opioid-dependent gravid women (26). In that study, the buprenorphine-exposed neonates required, on average, 89% less morphine to treat neonatal abstinence syndrome, a 43% shorter hospital stay, and a 58% shorter duration of medical treatment for neonatal abstinence syndrome (26). These results support the use of buprenorphine as a potential first-line medication for pregnant opioid-dependent women who are new to treatment. It is important to understand that buprenorphine will not be effective for all patients.

Women who become pregnant while already undergoing a treatment with a stable co-formulated buprenorphine dosage generally are advised to continue the same dosage but to transition to the single-agent product. The indications for the use of buprenorphine during pregnancy are in flux currently. Previous recommendations have limited use of buprenorphine to women who have refused to use methadone, have been unable to take methadone, or those for whom methadone treatment was unavailable. The current trend is moving toward considering a patient as a potential candidate for buprenorphine if she prefers buprenorphine to methadone, gives informed consent after a thorough discussion of relative risks and benefits, and is capable of adherence and safe self-administration of the medication. If the pregnant woman is receiving methadone therapy, she should not consider transitioning to buprenorphine because of the significant risk of precipitated withdrawal. The potential risk of unrecognized adverse long-term outcomes, which is inherent with widespread use of relatively new medications during pregnancy, should always be taken into consideration.

Medically supervised withdrawal from opioids in opioid-dependent women is not recommended during pregnancy because the withdrawal is associated with high relapse rates (27). However, if methadone maintenance is unavailable or if women refuse to undergo methadone or buprenorphine maintenance, medically supervised withdrawal should ideally be undertaken during the second trimester and under the supervision of a physician experienced in perinatal addiction treatment (13). If the alternative to medically supervised withdrawal is continued illicit drug use, then a medically supervised withdrawal in the first trimester is preferable to waiting until the second trimester.

It is important that frequent communication be maintained between the patient's obstetric care provider and the addiction medicine provider to coordinate care. The federal confidentiality law 42 CFR Part 2 applies to addiction treatment providers. Patient information release forms with specific language regarding substance use are required (28).

Intrapartum and Postpartum Management

Women receiving opioid-assisted therapy who are undergoing labor should receive pain relief as if they were not taking opioids because the maintenance dosage does not provide adequate analgesia for labor (29, 30). Epidural or spinal anesthesia should be offered where appropriate for management of pain in labor or for delivery. Narcotic agonist–antagonist drugs, such as butorphanol, nalbuphine, and pentazocine, should be avoided because they may precipitate acute withdrawal. Buprenorphine should not be administered to a patient who takes methadone.

Pediatric staff should be notified of all narcotic-exposed infants.

In general, patients undergoing opioid maintenance treatment will require higher doses of opioids to achieve analgesia than other patients. One study showed that after cesarean delivery, women who used buprenorphine required 47% more opioid analgesic than women who did not use buprenorphine treatment, but adequate pain relief was achieved with short-acting opioids and antiinflammatory medication (31). Injectable nonsteroidal antiinflammatory agents, such as ketorolac, also are highly effective in postpartum and postcesarean delivery pain control. Daily doses of methadone or buprenorphine should be maintained during labor to prevent withdrawal, and patients should be reassured of this plan in order to reduce anxiety. Dividing the usual daily maintenance dose of buprenorphine or methadone into three or four doses every 6–8 hours may provide partial pain relief; however, additional analgesia will be required (29).

Women should be counseled that minimal levels of methadone and buprenorphine are found in breast milk regardless of the maternal dose. Breastfeeding should be encouraged in patients without HIV who are not using additional drugs and who have no other contraindications (32). The current buprenorphine package insert advises against breastfeeding; however, a consensus panel stated that the effects on the breastfed infant are likely to be minimal and that breastfeeding is not contraindicated (33). Swaddling associated with breastfeeding may reduce neonatal abstinence syndrome symptoms, and breastfeeding contributes to bonding between mother and infant as well as providing immunity to the infant.

Although most pregnant women who receive methadone will experience dosage increases during pregnancy, and a need for dosage reduction might be expected, one study demonstrated little need for immediate postpartum methadone dosage reduction (34). Most women who undergo buprenorphine maintenance therapy will not experience large dosage adjustments during their pregnancies and may continue the same dosages after delivery (34). However, the postpartum patient who receives opioid therapy should be closely monitored for symptoms of oversedation with dosages titrated as indicated. Women should continue in their treatment and addiction support postpartum. Discussions of contraceptive options should begin during pregnancy and contraception, including long-acting reversible contraceptive methods, should be provided or prescribed before hospital discharge. Access to adequate postpartum psychosocial support services, including chemical dependency treatment and relapse prevention programs, should be ensured (33).

Neonatal Abstinence Syndrome

Although maternal methadone or buprenorphine therapy improves pregnancy outcomes and reduces risky behavior, its use puts the neonate at risk of neonatal abstinence syndrome, which is characterized by hyperactivity of the central and autonomic nervous systems (13). Infants with neonatal abstinence syndrome may have uncoordinated sucking reflexes leading to poor feeding, become irritable, and produce a high-pitched cry. In infants exposed to methadone, symptoms of withdrawal may begin at anytime in the first 2 weeks of life, but usually appear within 72 hours of birth and may last several days to weeks (13). Infants exposed to buprenorphine who develop neonatal abstinence syndrome generally develop symptoms within 12–48 hours of birth that peak at 72–96 hours and resolve by 7 days (35). Close communication between the obstetrician and pediatrician is necessary for optimal management of the neonate.

All infants born to women who use opioids during pregnancy should be monitored for neonatal abstinence syndrome and treated if indicated (13). Treatment is adequate if the infant has rhythmic feeding and sleep cycles and optimal weight gain (13).

Long-Term Infant Outcome

Recent data on long-term outcomes of infants with in utero opioid exposure are limited. For the most part, earlier studies have not found significant differences in cognitive development between children up to 5 years of age exposed to methadone in utero and control groups matched for age, race, and socioeconomic status, although scores were often lower in both groups compared with population data (36). Preventive interventions that focus on enriching the early experiences of such children and improving the quality of the home environment are likely to be beneficial (37).

Summary

Early identification of opioid-dependent pregnant women improves maternal and infant outcomes. Contraceptive counseling should be a routine part of substance use treatment among women of reproductive age to minimize the risk of unplanned pregnancy. Pregnancy in the opioid-dependent woman should be co-managed by the obstetrician–gynecologist and addiction medicine specialist with appropriate 42 CFR Part 2-compliant release of information forms. This collaboration is particularly important when the woman receives opioid maintenance treatment or is at high risk of relapse. When opioid maintenance treatment is available, medically supervised withdrawal should be discouraged during pregnancy. It is essential for hospitalized pregnant women who initiated opioid-assisted therapy to make a next-day appointment with a treatment program before discharge. Infants born to women who used opioids during pregnancy should be closely monitored for neonatal abstinence syndrome and other effects of opioid use by a pediatric health care provider.

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