

ABSTRACT: Opioid use in pregnancy has escalated dramatically in recent years, paralleling the epidemic observed in the general population. To combat the opioid epidemic, all health care providers need to take an active role. Pregnancy provides an important opportunity to identify and treat women with substance use disorders. Substance use disorders affect women across all racial and ethnic groups and all socioeconomic groups, and affect women in rural, urban, and suburban populations. Therefore, it is essential that screening be universal. Screening for substance use should be a part of comprehensive obstetric care and should be done at the first prenatal visit in partnership with the pregnant woman. Patients who use opioids during pregnancy represent a diverse group, and it is important to recognize and differentiate between opioid use in the context of medical care, opioid misuse, and untreated opioid use disorder. Multidisciplinary long-term follow-up should include medical, developmental, and social support. Infants born to women who used opioids during pregnancy should be monitored for neonatal abstinence syndrome by a pediatric care provider. Early universal screening, brief intervention (such as engaging a patient in a short conversation, providing feedback and advice), and referral for treatment of pregnant women with opioid use and opioid use disorder improve maternal and infant outcomes. In general, a coordinated multidisciplinary approach without criminal sanctions has the best chance of helping infants and families.

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Screening for substance use should be part of comprehensive obstetric care and should be done at the **first prenatal visit** in partnership with the pregnant woman. Screening based only on factors, such as poor adherence to prenatal care or prior adverse pregnancy outcome, can lead to missed cases, and may add to stereotyping and stigma. Therefore, it is essential that screening be universal.

Routine screening should rely on validated screening tools, such as questionnaires, including 4Ps, NIDA Quick Screen, and CRAFFT (for women 26 years or younger).

For chronic pain, practice goals include strategies to avoid or minimize the use of opioids for **pain management**, highlighting alternative pain therapies such as nonpharmacologic (eg, exercise, physical therapy, behavioral approaches), and nonopioid pharmacologic treatments.

For pregnant women with an opioid use disorder, **opioid agonist** pharmacotherapy is the recommended therapy and is preferable to medically supervised withdrawal because withdrawal is associated with high relapse rates, which lead to worse outcomes. More research is needed to assess the safety (particularly regarding maternal relapse), efficacy, and long-term outcomes of medically supervised withdrawal.

Infants born to women who used opioids during pregnancy should be monitored by a pediatric care provider for neonatal abstinence syndrome, a drug withdrawal syndrome that opioid-exposed neonates may experience shortly after birth.

Given the unique needs of pregnant women with an opioid use disorder, health care providers will need to consider modifying some elements of prenatal care (such as expanded sexually transmitted infection [STI] testing, additional ultrasound examinations to assess fetal weight if there is concern for fetal growth abnormalities, and consultations with various types of health care providers) in order to meet the clinical needs of the patient's particular situation.

Before prescribing opioids for their patients, obstetrician–gynecologists and other health care providers should ensure that opioids are appropriately indicated; discuss the risks and benefits of opioid use and review treatment goals; and take a thorough history of substance use and review the Prescription Drug Monitoring Program to determine whether patients have received prior opioid prescriptions.

Breastfeeding should be encouraged in women who are stable on their opioid agonists, who are not using illicit drugs, and who have no other contraindications, such as human immunodeficiency virus (HIV) infection. Women should be counseled about the need to suspend breastfeeding in the event of a relapse.

Access to adequate postpartum psychosocial support services, including substance use disorder treatment and relapse prevention programs, should be made available.

Effects of Opioid Use on Pregnancy and Pregnancy Outcome

The safety of opioids during early pregnancy has been evaluated in a number of observational studies. Earlier reports have not shown an increase in risks of birth defects after prenatal exposure to oxycodone, propoxyphene, or meperidine. An association between first-trimester use of codeine and congenital abnormalities has been found in some studies but not in others. The authors of one retrospective study observed an increased risk of several birth defects with the use of prescribed opioids by women in the month before pregnancy or during the first trimester. Another recent observational study found a possible association between use of opioids in the first trimester and neural tube defects, although not with codeine use specifically.

A recent meta-analysis that compared methadone and buprenorphine found no difference between the groups with respect to congenital malformations. In addition, the incidence of anomalies reported were similar to what would be expected in the general population. Overall, concern about a potential small increased risk of birth defects associated with opioid agonist pharmacotherapy during pregnancy should be weighed against the clear risks associated with the ongoing misuse of opioids by a pregnant woman.

During pregnancy, chronic untreated addiction to heroin is associated with lack of prenatal care, increased risk of **fetal growth restriction**, **abruptio placentae**, **fetal death**, **preterm labor**, and intrauterine passage of **meconium**. Additionally, untreated addiction is associated with engagement in high-risk activities, such as prostitution, trading sex for drugs, and criminal activities. Such behaviors expose women to STIs, violence, and legal consequences, including loss of child custody, criminal proceedings, or incarceration.

Pregnant women with opioid use disorder often suffer from co-occurring mental health conditions, particularly **depression**, **history of trauma**, **posttraumatic stress disorder**, and **anxiety**. More than 30% of pregnant women enrolled in a substance use treatment program screened positive for moderate to severe depression, and more than 40% reported symptoms of postpartum depression. In addition, they are at increased risk of use of other substances, including tobacco, marijuana, and cocaine. These women also often suffer from poor nutrition, and many have disrupted support systems leading to social service needs. Identifying these problems during pregnancy with referral for specialized multidisciplinary care is important to achieve optimal care for these women.

Screening for Opioid Use and Opioid Use Disorder in Pregnancy

Screening for substance use should be a part of comprehensive obstetric care and should be done at the first prenatal visit in partnership with the pregnant woman. Substance use disorders affect women across all racial and ethnic groups and all socioeconomic groups, and affect women in rural, urban, and suburban populations. Screening based only on factors such as poor adherence to prenatal care or prior adverse pregnancy outcome can lead to missed cases, and may add to stereotyping and stigma. Therefore, it is essential that screening be universal. 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.

Maintaining a caring and nonjudgmental approach, as well as screening when the patient is alone, are important and will yield the most inclusive disclosure. Obstetric care providers should protect patient autonomy, confidentiality, and the integrity of the patient–physician relationship to the extent allowable by laws regarding disclosure of substance use disorder. Physicians should be aware that reporting mandates vary widely and should be familiar with the legal requirements within their state or community. Routine screening should rely on validated screening tools, such as questionnaires including 4Ps, NIDA Quick Screen, and CRAFFT (for women 26 years or younger). These tools have been well studied and demonstrate high sensitivity for detecting substance use and misuse. They can be used in direct interview format by physicians as well as nonphysicians and can be streamlined into clinical practice by using computer-based approaches

Treatment

Opioid Agonist Pharmacotherapy

Since the 1970s, opioid agonist pharmacotherapy (also referred to as medication-assisted treatment), with methadone in combination with counseling and behavioral therapy, has been the standard treatment of heroin addiction during pregnancy.

The rationale for opioid agonist pharmacotherapy during pregnancy is multifold. Opioid agonist pharmacotherapy prevents opioid withdrawal symptoms and is shown to prevent complications of nonmedical opioid use by reducing relapse risk and its associated consequences. It also improves adherence to prenatal care and addiction treatment programs. Opioid agonist pharmacotherapy in combination with prenatal care has been demonstrated to reduce the risk of obstetric complications

Neonatal abstinence syndrome is an expected and treatable condition that can follow prenatal exposure to opioid agonists and requires collaboration with the pediatric care team for care of the infant.

Methadone

Methadone is dispensed on a daily basis by a registered opioid treatment program and should be part of comprehensive treatment, including addiction counseling, family therapy, nutritional education, and other medical and psychosocial services as indicated for pregnant women with opioid use disorder. Maternal methadone dosages are managed by addiction treatment specialists within registered opioid treatment programs, and communication between the obstetric team and the opioid treatment program facilitates good care. The methadone dosage may need to be adjusted throughout the pregnancy to avoid withdrawal symptoms, which include drug cravings, abdominal cramps, nausea, insomnia, irritability, and anxiety. Methadone has significant pharmacokinetic interactions with many other medications, such as antiretroviral agents, and can prolong the QTc interval in a dose-related fashion, which should be considered before new medications are introduced.

If a woman has been treated with a stable methadone dose before pregnancy, pharmacokinetic and physiologic changes that occur during pregnancy may require dose adjustments, especially in the third trimester. Because of metabolic changes in pregnancy, a single daily dosage may not control withdrawal symptoms over a 24-hour period. Rapid metabolism often develops during pregnancy, especially in the third trimester and in these cases, split dosages may be optimal. Not all women require dose increases during pregnancy, and dosage adjustments should be made on a clinical basis.

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 that may cause fetal stress and maternal drug cravings, which increase the likelihood of relapse and treatment discontinuation.

Several studies have examined the extent to which the maternal methadone dosage is related to the severity of neonatal abstinence syndrome. A systematic literature review and meta-analysis concluded that the incidence and duration of neonatal abstinence syndrome do not differ based on the maternal dosage of methadone treatment; therefore, attempts to minimize the methadone dose are not indicated as low doses are not consistently associated with milder or shorter NAS symptoms. Interestingly, some studies find lower rates of NAS when split dosing regimens of methadone are used

In most situations, pregnant women initiate methadone induction in a licensed outpatient opioid treatment program. Some obstetric services initiate opioid agonist therapy with methadone or buprenorphine in an inpatient setting. Although this may allow closer monitoring of medication response, it is not always necessary or available. In cases when a pregnant woman initiates methadone treatment as an inpatient, an arrangement should be made before discharge for next-day admission to an opioid treatment program so that there are no missed days. Patients started on buprenorphine as an inpatient may receive a prescription until their appointment with a licensed buprenorphine prescriber. Identification of the ongoing buprenorphine provider and scheduling of an appointment should be done before discharge.

With the exception of buprenorphine, it is currently illegal for a physician to write a prescription for any other opioids, including methadone, for the treatment of opioid use disorder outside of a licensed opioid treatment program (where medications are dispensed). Buprenorphine is the only opioid agonist currently approved for the treatment of opioid use disorder by prescription in an office-based setting. However, methadone and buprenorphine may be dispensed in a hospital setting by physicians without waivers.

Antepartum, Intrapartum, and Postpartum Care

Antepartum Care

Elements of prenatal care for women with opioid use or use disorder will depend on each patient's situation and comorbid conditions. Several issues to consider include the following:

Testing for **STIs** and other infectious agents such as **HIV, hepatitis B and C, chlamydial infection, gonorrhea, syphilis,** and **tuberculosis** should be considered. Repeat testing in the third trimester may be indicated if the woman is considered at increased risk. Hepatitis B vaccination is recommended for pregnant women who are HBsAg negative but at high risk of hepatitis B infection.

Screening for depression and other behavioral health conditions should be conducted.

In addition to an ultrasound examination for fetal assessment in mid-second trimester, consideration should be given to first-trimester ultrasonography for best determination of the estimated due date and an interval ultrasonographic assessment of fetal weight later in pregnancy if there is concern for fetal growth abnormalities.

Consultations with anesthesia, addiction medicine specialists, pain management specialists, pediatrics, maternal–fetal medicine, behavioral health, nutrition, and social services should be conducted as needed.

Use of other substances, particularly tobacco use, is common in women with opioid use disorder. Screening for and discussion about this and other substances is important, and cessation services should be offered.

Intrapartum Care

Women taking methadone or buprenorphine who are in labor should have their maintenance opioid agonist dose continued and should receive additional pain relief. Epidural or spinal anesthesia should be offered, when appropriate, for management of pain in labor or for delivery. Opioid agonist–antagonist drugs such as butorphanol, nalbuphine, and pentazocine should be avoided because they can precipitate acute withdrawal in patients taking an opioid agonist. Some patients who are physiologically dependent on opioids may not disclose their substance use and health care providers may, therefore, not be aware of their opioid use. Because of this, some units have opted to remove these medications from their formularies because of inadvertent precipitation of withdrawal. Buprenorphine should not be administered to a patient who takes methadone. Pediatric staff should be notified of all infants exposed to opioids to ensure appropriate screening for neonatal abstinence syndrome.

In general, patients taking methadone or buprenorphine will require higher doses of opioids to achieve analgesia than other patients because they are tolerant to their maintenance treatment dose. One study showed that after cesarean delivery, women who took buprenorphine required 47% more opioid analgesic than women who did not take buprenorphine, but adequate pain relief was achieved with short-acting opioids and antiinflammatory medication. 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 a woman's labor and postpartum hospital stay to prevent withdrawal, and patients should be advised of this plan in advance in order to reduce anxiety. Dividing the usual daily treatment 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 .

The pain management of intrapartum and postpartum patients on opioid agonist therapies can be challenging because of their increased drug tolerance and hypersensitivity to pain. When resources are available, a consultation with an anesthesiologist can be beneficial in pregnant women with substance use disorder or chronic opioid use to formulate a pain management plan tailored to the individual patient. A multimodal pain control approach with neuraxial analgesia and nonsteroidal antiinflammatory drugs and acetaminophen typically is needed to provide effective intrapartum and postpartum pain relief

Postpartum Care

Breastfeeding is beneficial in women taking methadone or buprenorphine and has been associated with decreased severity of neonatal abstinence syndrome symptoms, less need for pharmacotherapy, and a shorter hospital stay for the infant. In addition, breastfeeding contributes to attachment between a woman and her infant, facilitates skin-to-skin care, and provides immunity to the infant. Breastfeeding should be encouraged in women who are stable on their opioid agonist, who are not using illicit drugs, and who have no other contraindications, such as HIV infection. Women should be counseled about the need to suspend breastfeeding in the event of a relapse. The American Academy of Pediatrics recommends breastfeeding for women taking methadone and buprenorphine regardless of maternal dose, as transfer of these medications into breast milk is minimal.

In nursing women, the ultra-rapid conversion of codeine to morphine can result in high and unsafe levels of morphine in blood and breast milk. The U.S. Food and Drug Administration has strengthened the label warning to state that breastfeeding is not recommended while using medicines containing codeine or tramadol because of the potential for serious adverse effects in the infant due to opioid overdose. However, if a codeine-containing medication is considered the preferred choice, the risk and benefits of this drug and the reasoning behind the FDA warning should be discussed with each family.

Although most pregnant women who take methadone will experience dosage increases during pregnancy, and a need for dosage reduction might be expected postpartum, one study demonstrated little need for immediate postpartum methadone dosage reduction. Significant dose reductions postpartum should not be done routinely but should be titrated to signs and symptoms of sedation, particularly at the peak of the dose (2–6 hours). Most women taking buprenorphine will not experience large dosage adjustments during their pregnancies and most may continue the same dosages after delivery. Other medications that can produce sedation (eg, benzodiazepines, zolpidem, antihistamines) should be used with caution, as they may add to the risk of maternal respiratory depression

Women with substance use disorder should continue their opioid agonist pharmacotherapy postpartum. The postpartum period represents a time of increased vulnerabilities, and women with opioid use disorder relapse far more often in the postpartum period compared with during pregnancy. Triggers for relapse may include loss of insurance and access to treatment, demands of caring for the new baby, sleep deprivation, and threat of loss of child custody. Psychiatric disorders such as depression, anxiety, bipolar disorder, and posttraumatic stress disorder are prevalent among women with opioid use disorder. Screening for postpartum depression should be routine, and assessing for other comorbid mental health conditions should be considered if there is a prior history or if concern exists. Access to adequate postpartum psychosocial support services, including substance use disorder treatment and relapse prevention programs, should be made available. In addition, postpartum women with opioid use disorder should receive overdose training and preferably, coprescribing of naloxone for overdose prevention

Neonatal Abstinence Syndrome

Neonatal abstinence syndrome is a drug withdrawal syndrome that may result from chronic maternal opioid use during pregnancy and is an expected and treatable condition seen in 30–80% of infants born to women taking opioid agonist therapies 43 85. Neonatal abstinence syndrome is characterized by disturbances in gastrointestinal, autonomic, and central nervous systems, leading to a range of symptoms including irritability, high-pitched cry, poor sleep, and uncoordinated sucking reflexes that lead to poor feeding. In infants exposed to methadone, symptoms of withdrawal may begin anytime in the first 2 weeks of life, but usually appear within 72 hours of birth and may last several days to weeks 30. 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 50. Recent evidence indicates that other substances such as nicotine, selective serotonin reuptake inhibitors, and benzodiazepines may increase the incidence and severity of neonatal abstinence syndrome 72. Use of validated screening assessments such as the Finnegan Scale to diagnose neonatal abstinence syndrome and protocols that standardize treatment using methadone or morphine have been associated with improved outcomes for these infants 72. Each nursery should develop an evidence-based written policy to assess and treat an infant with neonatal abstinence syndrome, and women should be informed of key components of these policies (eg, any delayed discharge of the infant or reporting requirements). Families should be encouraged to visit and care for their infants and women should be supported in their effort to breast feed their infants, if appropriate. Several perinatal collaborative quality initiatives have developed valuable resources for health care providers and patients to optimize the diagnosis and treatment of neonatal abstinence syndrome and promote collaboration between obstetric and neonatal care providers