
Methadone

OPIOID USE DISORDER during pregnancy

Nonjudgmental identification and treatment can maximize maternal/fetal outcomes

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For 3 years, your mental health clinic has been treating Ms. J, age 23, for bipolar disorder. She is single, unemployed, lives alone, and receives Social Security disability assistance and financial support from her parents. She has been successfully maintained on aripiprazole, 15 mg/d, and citalopram, 20 mg/d, for 18 months. Six months ago she began to miss therapy sessions and physician visits.

Her parents inform Ms. J's therapist that she is "snorting oxycontin" with her new boyfriend. At her next visit Ms. J confirms she has been struggling to manage an opioid use disorder for more than 1 year, and requests help.

After you educate her about the diagnosis, pathophysiology, and treatment of opioid addiction, she chooses to include pharmacotherapy as part of her treatment. After informed consent, Ms. J agrees to take buprenorphine and naloxone, meet with her therapist weekly, and attend twice-weekly Narcotics Anonymous (NA) meetings. Over the ensuing months she is gradually inducted onto buprenorphine and naloxone, 12 mg, shows improved insight and motivation, provides negative urine drug screens, and demonstrates increased ability to manage her recovery. Two weeks later Ms. J tells you she may be pregnant but wants to continue buprenorphine and naloxone.

Opioid use disorder (OUD) during pregnancy is among the most difficult clinical scenarios to manage. The prevalence of OUD during pregnancy is largely unknown. However, stigma against pregnant patients with OUD is substantial.[1] This article briefly summarizes identification, assessment, and treatment of OUD during pregnancy.

continued

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Opioid use during pregnancy

Clinical Point

During screening, a nonjudgmental, empathic attitude may be more important than the specific questions you ask

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Table 1

The '4P's Plus' screen for substance use during pregnancy

Parents: Did either of your parents ever have a problem with alcohol or drugs?
Partner: Does your partner have a problem with alcohol or drugs?
Past: Have you ever drunk beer, wine, or liquor?
Pregnancy: In the month before you knew you were pregnant, how many cigarettes did you smoke? In the month before you knew you were pregnant, how many beers/how much wine/ how much liquor did you drink?
A positive screen results when a patient answers either of the 2 questions relating to pregnancy, indicating *any* alcohol or tobacco use in the month before she knew she was pregnant

Source: Reference 8

To avoid confusion with the term "physical dependence," we will use "opioid use disorder" instead of "opioid dependence." The DSM-5 Substance Use Disorders Workgroup recommends combining abuse and dependence into a single disorder of graded clinical severity; however, this has not been finalized.[2]

Early identification is crucial

Early identification of OUD in pregnant women can be challenging. Self-reports underestimate use[3] and shame, fear of prosecution or involvement of child welfare services, and guilt can further erode self-report. Women with OUD may have irregular menses and might not be aware of their pregnancy until several months after conception.[4] Also, women with OUD who are maintained on opioid agonist therapies may misinterpret early signs of pregnancy—such as fatigue, nausea, vomiting, headaches, and cramps—as withdrawal symptoms and may respond by increasing their opioid dosing, thus exposing their fetus to increased drug levels. Finally, many women with OUD experience amenorrhea as a result of their stressful, unhealthy lifestyle, which may preclude pregnancy despite sexual activity. When these women later enroll in an opioid maintenance program, their endocrine function may return to normal, leading to unexpected pregnancy.[5]

Screening for OUD in pregnant patients has not been well studied. An interviewer's nonjudgmental, empathic attitude may be more important than the specific questions he or she asks. It may be best to begin with less threatening questions and proceed to more specific questions after developing a therapeutic alliance.[6]

Chasnoff et al[7] studied >2,000 Medicaid-eligible pregnant patients from 9 prenatal clinics to identify risk factors for substance use during pregnancy. Alcohol or tobacco use in the month before pregnancy most differentiated current drug or alcohol use from nonuse while pregnant; however, a wide variation in use rates among patients in this study limits the generalizability of these findings. Consider OUD in women with:

- physical examination findings or history that suggests substance use or withdrawal symptoms
- positive drug test results for illicit or nonprescribed opioids
- aberrant medication-taking behaviors in those receiving prescribed opioids
- nicotine or alcohol use in the month before they knew they were pregnant
- a history of addiction-related disorders
- evidence of diseases associated with drug use, such as human immunodeficiency virus or hepatitis C
- poor prenatal care attendance
- unexplained fetal growth abnormalities.

Chasnoff et al demonstrated the reliability and effectiveness of a 1-minute, 5-item instrument (the "4 P's Plus") to screen for substance use, including heroin, during pregnancy (***Table 1***).[8] In a study of 228 pregnant women, the overall internal consistency of this instrument was low but acceptable. More than three-quarters of patients (78%) were correctly classified as positive or negative, sensitivity was 87%, specificity was 76%, negative predictive validity was extremely high (97%), and positive predictive validity was low (36%). This low positive predictive validity may

be acceptable in this population because over-identification of women at risk may be preferred to under-identification. The 4 P's Plus identifies light and infrequent substance users who otherwise would go undetected, although it may place undue burden on providers to follow up on what later may be revealed to be a false positive screen.[9] OUD-specific screening approaches are lacking; screening for general substance use is discussed elsewhere in the literature.[10]

A combination of interviewing and biologic drug screening may be more effective than either approach alone.[11] Drug screening should include opioids typically screened for (morphine, codeine, heroin metabolite) and those for which additional tests may be required (eg, semi-synthetics such as oxycodone and synthetics such as fentanyl). Learn your state's civil mandates regarding drug-using pregnant women, guidelines for addiction treatment, and confidentiality provisions, especially as they relate to drug testing and mandatory reporting. Ideally, patients should be informed of these issues before they undergo drug testing or other procedures. These requirements may vary according to physician specialty or role in providing care.

Diagnosis of opioid dependence is based on DSM-IV-TR criteria; however, the proposed DSM-5 criteria for OUD may better emphasize cautions about including tolerance or withdrawal when diagnosing OUD in the setting of medically supervised and appropriate opioid use.[2]

Stigma against pregnant women with OUD easily can erode therapeutic efforts. Perhaps the most important element of assessment is maximizing the therapeutic alliance to ensure that the patient complies with prenatal obstetric care and maternal addiction services. Pregnancy may be an opportune time to motivate women with OUD to make a change because they may be more open to receiving help.[12] Motivational interventions are helpful for many but not all patients; the best approach to such interventions is still uncertain.[13] Regardless of the mother's motivation, prenatal care is fundamental.

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 acuminata • herpes • HIV/AIDS • syphilis
Tetanus
Cystitis
Pyelonephritis

AIDS: acquired immune deficiency syndrome; HIV: human immunodeficiency virus

Source: Reference 6

Office management

OUD-specific treatment decreases opioid use and improves birth outcomes[14]; however, retaining these patients in treatment can be difficult. Addressing social issues—including financial burdens, unstable living conditions, intimate partner violence, transportation difficulties, and limited access to medical and child care—can facilitate treatment.[5] The Addiction Severity Index version tailored to women and pregnancy[15] examines 7 domains of functioning (drugs, alcohol, psychological, social, medical, legal, and employment), informs treatment planning, quantifies treatment progress, and has predictive validity.[16] Services are more likely to be effective if started during pregnancy as opposed to after delivery. Although detoxification is possible under carefully monitored conditions, many women relapse after detoxifying, and neonatal abstinence syndrome (NAS)—a

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For women with OUD, the risks of detoxification often outweigh the benefits

Opioid use during pregnancy

Clinical Point

The first goal of pharmacotherapy for women with OUD is to reduce physical stress associated with fluctuating opioid blood levels

Table 3

Obstetric complications in women 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

Source: Reference 6

disorder in which an addicted newborn experiences drug withdrawal—is common. Therefore, the risks of detoxification often outweigh benefits.[5,17,18]

Rehabilitation services for the mother can be provided at various levels of care, including outpatient, intensive outpatient, day hospital, residential, and inpatient. Although pregnancy-specific OUD treatment is ideal, it may not be available. Clinicians should attempt to locate services that can incorporate resources for pregnant women. Providing a means for child care during treatment is paramount to compliance. Develop a plan for nonconfrontational counseling, job skills training/education, and ongoing care after delivery (including child care and transportation resources) at the onset of treatment. The length of time maintained in treatment is one of the strongest predictors of abstinence.[5]

Pregnant women with OUD should be screened for comorbid medical, obstetric, and psychiatric complications and referred accordingly (***Table 2, page 37*** and ***Table 3***).[6] Coordination among the patient's psychiatrist, primary care provider, and obstetrician/gynecologist is essential. Programs that integrate these approaches into a single treatment team may be ideal. Although pregnancy per se may not be associated with higher risk of mental disorders, the risk of major depressive disorder may be increased during the postpartum period.[19] Young, unmarried women with recent stressful life events, complicated pregnancies, and poor overall health may face a significantly increased risk of psychiatric illness during pregnancy.[19] Patients whose opioid use has caused pregnancy complications may experience guilt and grief.

Increased education and screening for substance use as the pregnancy approaches term is necessary because patients may mistake early labor for symptoms of opioid withdrawal or worry that delivery room pain management will be inadequate and therefore relapse. Among pregnant women with addiction, preterm labor may be most common in those with OUD.[12]

Opioid agonist therapy

Obstetric complications in women with OUD may be related to rapid, frequent fluctuations of opioid blood levels during intoxication and withdrawal. Therefore, the first goal of pharmacotherapy is to reduce physical stress associated with cycling opioid blood levels. Opioid agonist medications can be extremely effective. Opioid agonist treatment for pregnant patients is similar to that of nonpregnant patients but includes pregnancy-specific objectives (***Table 4, page 40***).[20]

Few anti-relapse medications have been studied in pregnant patients. Pharmacotherapies for OUD include methadone and buprenorphine. In our experience, opioid antagonists such as naltrexone typically would not be considered for pregnant patients because:

- their expected efficacy in reducing relapse in pregnant patients is lower than that of other medications
- their expected risk for inducing withdrawal is higher compared with methadone or buprenorphine
- research on the use of naltrexone during pregnancy is lacking.

Methadone has been used to treat OUD during pregnancy since the late 1970s.[5] It requires adherence to strict federal regula-

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Opioid use during pregnancy

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Methadone dosages should be based on a woman's relapse risk, experience with methadone, and other factors

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Visit this article at CurrentPsychiatry.com for a discussion of breast-feeding during opioid maintenance

Table 4

Opioid agonist treatment objectives for addicted patients who are pregnant

General objectives
Prevent opioid withdrawal signs and symptoms
Provide a comfortable induction onto the medication
Block the euphoric and reinforcing effects of illicit opioids while also attenuating the motivation (craving, social interactions) to use illicit opioids and other drugs
Enhance treatment retention
Create a more optimal environment for behavioral and psychosocial interventions
Pregnancy-specific objectives
Eliminate or reduce fetal exposure to illicit opioids and other illicit drugs
Stabilize the intrauterine environment
Enhance involvement in prenatal care
Create an optimal environment to address pregnancy-specific problems

Source: Reference 20

tions and is FDA pregnancy class C (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate well-controlled studies in humans, but potential benefits may warrant use in pregnant women despite potential risks). Pregnant women have been safely maintained on methadone without adverse long-term maternal or fetal effects, and the National Institutes of Health recommends it as the standard of care for pregnant women with OUD. A woman steadily maintained on methadone is more likely to have a healthy pregnancy and infant than a woman who uses alcohol or other drugs.[21] Further, the structure and services of methadone maintenance treatment can improve compliance with prenatal care and help prepare patients for parental responsibilities.

Fluctuating blood opioid levels are minimized when methadone dosage is individually determined. Dosages should be based on a woman's stage of pregnancy, relapse risk, pre-pregnancy methadone dose, experience with methadone, and clinical history. Some women experience lowered methadone blood levels during pregnancy because of increased fluid space, a larger tissue reservoir that can store methadone, and increased drug metabolism by both placenta and fetus. As a result, increased or split (twice daily) dosing may be indicated.[22-24]

Buprenorphine is FDA pregnancy class C. Although not approved for use during pregnancy, it has been used successfully for pregnant patients with OUD.[12,25] It is a partial agonist of the mu opioid receptor and an antagonist of the kappa opioid receptor, which may reduce its abuse liability and NAS severity.

The few randomized clinical trials comparing methadone with buprenorphine during pregnancy suggest that buprenorphine is not inferior to methadone in safety and discomfort of induction from a short-acting opioid, nor in outcome measures assessing NAS and maternal and neonatal safety.[26,27] Results from the recent Maternal Opioid Treatment: Human Experimental Research project suggest that buprenorphine may have some advantages over methadone in pregnancy. Buprenorphine-maintained neonates may need less morphine, have shorter hospital stays, and require shorter treatment for NAS.[28] However, treatment retention may be lower for buprenorphine-maintained mothers; any resultant long-term consequences on maternal and child health are as yet unexplored. These findings require replication.

Methadone and buprenorphine are not interchangeable. Many patients maintained on methadone do not respond optimally to buprenorphine. Clinics that dispense maintenance methadone are required to provide counseling services and random drug testing; these requirements do not apply to physicians who prescribe buprenorphine. Moreover, in our experience buprenorphine at times has been prescribed without close regard to psychosocial issues, adequate random drug testing, or coordination of care with other providers.

In pregnant patients, buprenorphine is preferred over buprenorphine and naloxone to avoid fetal exposure to naloxone, which may cause intrauterine withdrawal and maternal-fetal hormonal changes. To

reduce abuse or diversion, patients should undergo drug testing to ensure buprenorphine is present, smaller prescriptions may be provided, and tablets can be counted. Limited data suggests buprenorphine is not teratogenic. Some data show low placental transfer of buprenorphine, thereby limiting fetal exposure and lowering risk for intrauterine growth restriction.[29]

Delivery and postnatal care

Compared with those not in treatment, women who are engaged in a multidisciplinary treatment program at the time of delivery demonstrated higher gestational age, increased birth weights, and lower rates of neonatal ICU admissions. They also realized a cost savings of $4,644 per mother-infant pair.[30]

During delivery, pain medication should not be withheld solely because a pregnant woman has a history of addiction-related disorders; these women are subject to pain during delivery as much as other women. Avoid using mixed agonists/antagonists such as nalbuphine or butorphanol in women receiving opioid maintenance medication. Labor and delivery pain management for a pregnant patient maintained on opioid agonist therapies is discussed elsewhere in the literature.[31] Every effort should be made to ensure that the mother remains in treatment through delivery and beyond.

To read about advising women with OUD on the benefits and risks of breastfeeding while receiving opioid agonist maintenance treatment, see this article at CurrentPsychiatry.com.

CASE CONTINUED

Medication change

Ms. J's boyfriend has left her and her parents have not readily accepted her pregnancy and need for support. She continues to attend NA meetings and weekly therapy. After educating her about the differences between buprenorphine and buprenorphine and naloxone in relation to risk, benefits, and side effects, you switch Ms. J to buprenorphine, 12 mg/d, while maintaining her on aripiprazole and citalopram. She consents to exchanging information about her medical, mental health, and addiction-related treatment with her primary care provider, who helps locate an obstetrician/gynecologist comfortable with her OUD and buprenorphine. Ms. J's therapist helps link her with social services agencies to ensure prenatal care, assist with removing barriers to care, and plan for her needs as a parent.

After checking your state's mandates, you determine you are not required to report Ms. J's drug testing results. Ms. J's ongoing drug testing shows the presence of buprenorphine and the absence of other opioids and all drugs of abuse.

Ms. J's delivery is uncomplicated medically; however, family, financial, and parental role issues remain problematic. Encouraging her involvement in therapy and social services as part of her continued buprenorphine prescribing proves beneficial.

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Clinical Point

Buprenorphine may have some advantages over methadone during pregnancy but more research is needed

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Related Resources

- Jones HE, Martin PR, Heil SH, et al. Treatment of opioid dependent pregnant women: clinical and research issues. J Subst Abuse Treat. 2008;35(3):245-259.
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Drug Brand Names

Aripiprazole • Abilify
Buprenorphine and naloxone • Suboxone
Buprenorphine • Subutex
Butorphanol • Stadol
Citalopram • Celexa
Fentanyl • Duragesic, Sublimaze, others
Methadone • Dolophine
Naloxone • Narcan
Naltrexone • ReVia
Nalbuphine • Nubain
Oxycodone • Oxycontin

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Clinical Point

During delivery, pain medication should not be withheld solely because a woman has a history of addiction-related disorders

Bottom Line

Opioid use disorder in pregnant women should be identified early to maximize maternal-fetal outcomes. Identification and assessment involves establishing a therapeutic alliance, history-taking, and drug testing. Removing barriers to care and considering opioid maintenance therapy is central. Legal mandates regarding reporting drug use by pregnant women vary by state.

Box

Breast-feeding: OK while receiving opioid agonist treatment

Methadone is compatible with breast-feeding[a] and the American Academy of Pediatrics[b] and World Health Organization[c] recommend breast-feeding for women receiving methadone unless there are contraindications such as human immunodeficiency virus infection.[a] Instruct mothers to seek medical advice if their breast-fed infant appears sedated.[b] Because the amount of methadone in breast milk is very small and depends on the methadone dose, the breast milk of mothers receiving methadone may be insufficient to prevent neonatal abstinence syndrome (NAS) and infants still may require opioid agonist treatment.[d]

Although breast-feeding by mothers receiving buprenorphine is not recommended by the drug's manufacturer, there is consensus that buprenorphine is found in low levels in breast milk[e,f] and is compatible with breast-feeding.[g] Because of partial agonism and low oral bioavailability, buprenorphine may not suppress NAS from methadone withdrawal. Always obtain appropriate informed consent.

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