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Review

Opioid Use Disorder in Pregnancy

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Opioid use disorder (OUD) in pregnancy has increased significantly in the past 10 years. Women with OUD may often be undertreated or untreated because of limited accessibility to treatment, particularly in rural areas. Because detoxification is not recommended during pregnancy due to the potential for adverse outcomes in the fetus and a high risk of relapse for the woman, more primary care providers need to be well versed in opioid-assisted therapy. In addition, recent changes in Food and Drug Administration regulations now allow nurse practitioners and physician assistants with specialized training to provide buprenorphine treatment for pregnant women with OUD in primary care settings. The purpose of this article is to provide information and guidance for clinicians working with and treating this population.
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INTRODUCTION

The number of women who use opioids during pregnancy has increased significantly in the United States during the last decade. This includes women who misuse prescription opioids, both legally and illicitly, as well as those who use heroin. Currently, approximately 5.8 of 1000 pregnancies in the United States are complicated by the use of opioids, although rates vary widely by region.[1] Women with opioid use disorder (OUD) have higher per-hospitalization costs, have higher rates of extended hospital stay, and are almost 4 times more likely to die before discharge than women not using opioids.[2] Psychiatric comorbidity is also common in OUD, as a significant number of women who become dependent on or addicted to opioids have a history of emotional and/or physical trauma, including childhood abuse and neglect, sexual assault, and intimate partner violence.[3,4] Although the prevalence of psychiatric comorbidity in pregnant women with OUD is not well established, some studies have reported an incidence as high 65% to 75%, particularly for mood disorders such as anxiety and depression.[4,5] To further complicate the clinical situation, pregnant women with OUD face both stigmatization and multiple barriers to care. They are often reluctant to seek treatment due to fear of criminal prosecution or child welfare consequences, because at least 18 states consider substance abuse during pregnancy to be child abuse.[6,7] These barriers frequently result in little to no prenatal care and poorer birth outcomes, and low-income women and women of color are disproportionately affected.[7] Untreated or undertreated pregnant women experience high rates of relapse and worse health outcomes as a result of repeated opioid withdrawal cycles during pregnancy.[8,9] These withdrawal cycles also have deleterious effects on the fetus and can result in preterm labor, fetal distress, or fetal demise.[9]

Ideally, maternity care for women with OUD should be managed in the context of a comprehensive, multidisciplinary care program that includes substance abuse counselors, social workers, case managers, psychiatrists, and opioid replacement therapy providers.[3,8] However, there are few providers in the United States who have both perinatal care and addiction treatment expertise,[6] and only 19 states have funded drug treatment programs designed for pregnant women.[10] Given the shortage of specialized care programs and providers, particularly in rural areas, the majority of pregnant women with OUD are cared for by various primary care clinicians, including obstetricians, family practice physicians, family and women's health nurse practitioners (NPs), certified nurse-midwives (CNMs), and physician assistants (PAs). Thus, there is an increased need for further provider training and education in this area of practice.[11] Recent federal legislation (the Comprehensive Addiction and Recovery Act [CARA]) in 2016 authorized NPs and PAs to undertake specialized training to prescribe buprenorphine (Subutex) for opioid-assisted therapy.[12,13] Although CNMs were not included in this initial legislation (unless they were dually certified as an NP or PA), it is possible that this situation may change in the near future (Jesse Bushman, MS, American College of Nurse-Midwives, written communication, July 22, 2016).

The purpose of this article is to provide evidence-based education on OUD for advanced practice registered nurses (APRNs), PAs, and CNMs who care for pregnant women in primary care settings. A secondary purpose is to offer guidance to those APRNs who are currently, or interested in becoming, authorized to prescribe buprenorphine for opioid replacement therapy. It should be recognized, however, that some women presenting to primary care settings will require a higher level of addiction care than these clinicians can accommodate. These women should be referred to a specialized program in order to ensure optimal care.

PHARMACOLOGY OF OPIOID DRUGS

The terms *opiate* and *opioid* are often used interchangeably. However, *opiate* is an older term that refers to drugs that are naturally derived from the opium poppy, such as morphine or heroin. The term *opioid,* a more recent designation, is commonly used to designate both natural and synthetic substances that bind to opioid receptors (including antagonists).[14] In this article, the term *opioid* will be used to refer to all drugs in this class.

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Quick Points

- Untreated or undertreated pregnant women with opioid use disorder experience high rates of relapse and worse health outcomes as a result of repeated opioid withdrawal cycles during pregnancy.
- Because detoxification is not recommended during pregnancy due to the high risk of relapse in the woman and the potential for adverse outcomes in the fetus, more primary care providers need to be well educated about opioid replacement.
- Primary care providers, including obstetricians, family practice physicians, family and women's health nurse practitioners, certified nurse-midwives, and physician assistants, can successfully care for this population with additional training and education.

Opioids are classified as naturally occurring, semisynthetic, and synthetic. Examples of naturally occurring opioids are heroin, morphine, and codeine. Semisynthetic opioids include hydrocodone (Vicodin), oxycodone, oxymorphone (Opana), buprenorphine, and hydromorphone (Dilaudid). Synthetic opioid examples are methadone (Dolophine), fentanyl (Duragesic), meperidine (Demerol), and tramadol (Ultram).[15] Examples of a drug from each class are discussed individually under the headings to follow.

When an opioid binds to a neuron membrane receptor, the cell becomes hyperpolarized as a result of the closure of calcium channels and opening of potassium channels. The charge differential decreases the likelihood of the neuron firing in response to a specific action potential. Sensory neurons decrease their activity, resulting in fewer afferent sensory signals returning to the central nervous system, leading to decreased pain sensation.[16] Although up to 17 different classes of opioid receptors have been identified in the human body, there are 3 general classes common in the discussion of opioids: delta, kappa, and mu. The response of the receptors to an opioid is based on the affinity to bind to a particular opioid receptor. For example, morphine predominantly binds to and activates with mu receptors in the central nervous system, with a high potential to elicit analgesia, euphoria, sedation, respiratory depression, and/or physical dependence.[17]

Once physical opioid dependence has occurred, a withdrawal syndrome develops with cessation of opioid use. Women using short-acting opioids (eg, heroin) may develop withdrawal syndrome within 4 to 6 hours of use, which often continues up to 72 hours. Physical symptoms will typically resolve within 7 days. With long-acting opioids (eg, methadone), withdrawal syndrome occurs within 24 to 36 hours and may last for several weeks. Relapse is often attributed to obsessive thinking and drug craving, which can last for years.[14]

Heroin (Naturally Occurring Opioid)

Illegal in the United States but used therapeutically in some parts of the world, heroin (diacetylmorphine) is a naturally occurring opioid that is rapidly metabolized to morphine. Ingestion is most commonly either by smoking or intravenous use, although it may be administered by snorting, suppository (rectal or vaginal), or orally.[18] It typically induces an intense euphoria with a rapidly developing tolerance requiring increasing doses to achieve the same level of effect. Two to 8 mg of heroin usually have a duration of 4 to 6 hours.[17] Heroin injection is associated with comorbid conditions, including HIV infection (60%), hepatitis B and C infection (60%-80%), and tuberculosis.[19]

Buprenorphine (Semisynthetic Opioid)

Buprenorphine is a mu partial agonist. It is also a kappa and delta receptor antagonist, with a possible decrease in sensation of "drug reward."[9] Buprenorphine is indicated for both opioid replacement therapy and analgesia. Bioavailability is 30% sublingually and 48% intranasally,[20,21] and it is primarily metabolized by the liver (cytochrome P[CYP]450), with a variable half-life of 20 to 44 hours (average, 37 hours). Dosage adjustments are required in hepatic dysfunction but not in renal deficiency. Adverse reactions include nausea, vomiting, urinary retention, sedation, mild potential for respiratory depression, and constipation but tend to be less intense than full agonist opioids.[20] The primary precaution in the initiation of buprenorphine therapy is that it can precipitate mild opioid withdrawal symptoms, but they are usually easily tolerated.[9]

Methadone (Synthetic Opioid)

Methadone is a mu opioid agonist with a greater efficacy than morphine with repeat dosing. It is also an N-methyl-D-aspartate (NMDA) receptor antagonist, potentially decreasing central nervous system pain thresholds, which lowers the risk of developing tolerance.[17] Other nonopioid actions include inhibition of monoamine (includes serotonin and norepinephrine) reuptake, which, with NMDA antagonist activity, increases analgesia.

Methadone is indicated for both analgesia and opioid replacement therapy. The bioavailability is 80% for oral dosing. It has a high binding affinity for muscle, renal, hepatic, and brain tissues, with slow tissue release for weeks after discontinuation. Methadone is primarily metabolized in the liver (CYP450), with a variable half-life of 8 to 59 hours, depending on an individual's metabolism.[22] Because of the physiologic changes of pregnancy, however, the half-life of methadone decreases from an average of 22 to 24 hours to 8 hours, requiring dosage adjustments as gestation progresses.[9] Adverse reactions include pruritus, nausea, constipation, sedation, potential for respiratory depression, and excessive flushing or sweating.[22,23] Other issues to consider in the use of methadone are the potential for electrocardiogram (ECG) changes related to dosage and drug-to-drug interactions. An ECG should be performed before initiating methadone

Table 1. *Diagnostic and Statistical Manual of Mental Disorders* (5th ed) Diagnosis of Opioid Use Disorder

Definition
A problematic pattern of opioid use leading to clinically significant impairment or distress. This pattern occurs within a 12-month period and includes 2 or more of the following criteria.
Diagnostic criteria[a]
Opioids are taken in larger amounts or over a longer period than was intended.
There is a persistent desire or unsuccessful attempts to cut down or control opioid use.
A great deal of time is spent in activities necessary to obtain, use, or recover from use of opioids.
Craving or a strong desire or urge to use opioids.
Recurrent opioid use resulting in a failure to fulfill major role obligations at home, work, or school.
Important social, recreational, or occupational activities are given up or reduced because of opioid use.
Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
Recurrent opioid use in situations in which it is physically hazardous.
Continued opioid use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
Tolerance as defined by either of the following:
A need for markedly increased amounts of the opioid to achieve intoxication or desired effect
or
A markedly diminished effect with continued use of the same amount of opioid
Withdrawal as manifested by either of the following:
The characteristic opioid withdrawal syndrome
or
An opioid or a closely related substance is taken to relieve or avoid withdrawal symptoms

Source: American Psychiatric Association.[24]
[a]Note: These criteria are not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

treatment and periodically in any patient dosed in excess of 100 mg per day. Postpartum dosing will likely need to be reduced due to decreased maternal metabolism focused on moderating for symptoms of somnolence.[8–11]

OPIOID USE DISORDER AND PHYSIOLOGY OF ADDICTION

Although OUD can develop at any age, it typically begins in the late teens or early 20s. The disorder is characterized by periods of abstinence and relapse, and usually continues over a period of many years.[24] Diagnostic characteristics of OUD are listed in Table 1. Even with treatment, relapse is common. Approximately 20% to 30% of people with OUD achieve long-term abstinence. There is a decreased prevalence after the age of 40 due either to early mortality or remission of symptoms, that is, "maturing out."[24] Common terms associated with OUD are included in Table 2.

Since the late 1990s, OUD and other substance abuse disorders have been conceptualized as a chronic, underlying change in brain circuitry that persists for years, even after detoxification. The hypothesis of the "brain disease model of addiction" (BDMA) is that drugs such as opioids target the brain's reward system by flooding the brain with 2 to 10 times the amount of dopamine that would normally be released in other pleasurable activities, such as eating and sex.[25] The dopamine surge has a powerful effect on the reward circuits in the brain and encourages the individual to continue to seek this euphoric effect, leading to intense drug craving and, ultimately, tolerance. Behavioral effects of these brain changes result in cycles of relapse and drug craving and may persist for years. Long-term exposure to the drug can alter brain circuitry to the point that the person may experience uncontrollable cravings whenever they are exposed to these cues, even after many years of abstinence.[25] Although the brain disease model is widely accepted as an explanatory model of addiction, other neuroscientists argue that it is primarily applicable to a minority of individuals with severe addiction.[26]

TERATOGENIC AND PREGNANCY OUTCOME EFFECTS

Teratogenic and pregnancy outcome effects are difficult to study in humans because most of the available research is limited by maternal self-report and/or concurrent use of multiple substances. With the exception of fetal alcohol syndrome, there has been no specific birth defect syndrome described for any illicit or prescription drug of abuse.[27] However, fetuses exposed to opioids in utero have been found to have a higher likelihood of birth defects. The National Birth Defects Prevention Study[28] reported statistically significant associations between opioids and several major defects in the interval from one month prior to 3 months after conception.[28] The most common defects included conoventricular septal defects (odds ratio [OR], 2.7; 95% confidence interval [CI], 1.1-6.3),

Table 2. Definition of Terms Relevant to Opioid Use Disorder

Term	Definition
Addiction	A chronic relapsing brain disorder involving compulsive use of drugs/substances despite adverse consequences, including harmful or self-destructive behaviors.[61] There is a high incidence of relapse after withdrawal. There are varying degrees of how the substance(s) may affect a person's behavior.[24,61]
Medication-assisted therapy	The combination of counseling and behavioral therapies with medications to treat substance abuse disorders and prevent opioid overdose.[10]
Neonatal abstinence syndrome or neonatal opioid withdrawal syndrome	A cluster of symptoms in a neonate in opioid withdrawal instigated by maternal untreated opioid use disorder, medication-assisted therapy patients still using opioids, use of prescriptive opioids, and patients treated with methadone or buprenorphine. Symptoms include convulsions, tremor, increased muscle tone, changes in postprandial sleep patterns, and excessive high-pitched cry, usually within 24 to 72 hours postpartum.[1]
Opioid use disorder	A pattern of opioid use leading to clinically significant distress or impairment (see the criteria for opioid use disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition).[24]
Physical dependence	The physical dependence on a substance requiring an increasing amount to achieve intoxication or a desired effect (tolerance). Withdrawal occurs on sudden discontinuation. Dependence may occur with chronic use of many drugs, including prescriptive medications taken appropriately as directed under medical supervision. Physical dependence does not indicate addiction but often is a part of addiction.[24,61]
Psychological dependence	The emotional and mental preoccupation with obtaining a substance to satiate a persistent craving for it. It is often the most common symptom of withdrawal. The pattern and frequency of use may differ considerably from person to person.[61]
Substance abuse	The continued use of a substance, including alcohol, illegal drugs, and/or the use of prescriptive drugs or over-the-counter medications with negative consequences. Negative consequences may include problems at home, school, or work; with interpersonal relationships; and/or with the legal system.[61]

Sources: Patrick et al,[1] Saia KA et al,[10] American Psychiatric Association,[24] National Institute on Drug Abuse.[62]

atrioventricular septal defects (OR, 2.0; 95% CI, 1.2-3.6), hypoplastic left heart syndrome (OR, 2.4; 95% CI, 1.4-4.1), spina bifida (OR, 2.0; 95% CI, 1.3-3.2), and gastroschisis (OR, 1.8; 95% CI, 1.1-2.9).[28] It should be recognized, however, that an increased relative risk for any birth defect still represents a very low absolute risk. For example, a 2.4-fold increase in hypoplastic left heart syndrome (prevalence, 2.4/10,000) would translate to a risk of 5.8/10,000 (0.06%), which is a very low absolute risk.[28]

Prenatal opioid use has also been associated with a higher risk of complications, including preterm birth, preterm premature rupture of membranes, intrauterine growth restriction, chorioamnionitis, meconium-stained amniotic fluid, neonatal abstinence syndrome (NAS), and perinatal death.[29,30] Prevalence of these complications, however, is difficult to determine due to inconsistency in findings among various studies.[27,31] For example, a 2011 Canadian study of 482 First Nations mother-infant pairs found an increased prevalence of preterm birth in neonates (8.2% vs 2.3%) exposed to oxycodone in pregnancy.[32] Conversely, in a US cohort of 2748 mother-infant pairs studied by Smith et al,[33] there was no association identified between opioid exposure and the prevalence of preterm birth. Furthermore, women who use opioids illicitly during pregnancy often experience poverty, violence, poor nutrition, smoking, lack of prenatal care, and other social challenges which confound analyses of complication rates.[27,31,33]

More consistent data are available for mother-infant pairs who participated in opioid-replacement therapy programs. Compared with pregnant women who used heroin alone, women on methadone have lower fetal death rates and higher infant birth weights.[30] NAS has been found to be more severe with methadone use than with either heroin or buprenorphine, however.[30] Methadone use in pregnancy is also associated with low birth weight, small for gestational age, reduced head circumference, and preterm birth compared with nonopioid-exposed pregnancies.[34,35] More recently, researchers have focused on comparing birth outcomes and NAS severity with the use of methadone versus buprenorphine. In a widely cited randomized controlled trial (the MOTHER study), Jones et al[36] reported that buprenorphine-exposed neonates had higher birth weights (mean, 3094 vs 2879 g), longer birth lengths (mean, 50 vs 48 cm), were less likely to be preterm (OR, 0.3; 95% CI, 0.1-2.0), required less morphine (mean dose, 1.1 vs 10.4 mg), had shorter hospital stays (10 vs 17.5 days), and had a shorter duration of

NAS treatment (4.1 vs 9.9 days) than methadone-exposed neonates. Similar findings have been reported in other large cohort studies from both the United States and Europe, which in turn has increased interest in the use of buprenorphine for opioid-assisted therapy in pregnancy.[37–39] With regard to long-term effects of prenatal opioid exposure in children, few longitudinal studies exist. Although a 2015 study by Nygaard et al[40] demonstrated that these children have some cognitive deficit that does not appear to improve over time, more research is needed to substantiate this claim.

PRENATAL CARE

Women with OUD often avoid prenatal care because of the stigma associated with drug abuse.[3,10,27,41,42] To encourage engagement in prenatal care, it is vitally important that providers and office staff maintain a compassionate and nonjudgmental attitude. By focusing on the woman as a person rather than solely on her opioid use, providers can build trust and rapport.[3,41] The more comfortable women with OUD feel in the clinic environment, the more likely they will be to disclose an accurate history and to engage in prenatal care.[41] Often, pregnancy is a good window of opportunity to motivate the woman to accept treatment. Providers and staff should also recognize that caring for women with OUD requires more time and resources.[3] Missed appointments, transportation difficulties, and longer clinic visits are common in this population.[42]

Screening for Substance Abuse

All clinicians who provide prenatal care should screen every woman for substance abuse routinely using a validated screening tool.[3,41,43] This practice helps to identify women with sporadic but clinically significant substance abuse.[3] Because women with OUD may arrive at dependency or addiction through legitimate prescriptions written by their health care providers, they may not realize the extent of the health risks and potential legal implications of their opioid use.[11] Thus, it is important to normalize the practice of substance abuse screening within the context of prenatal care to identify women using substances early[11] and avoid stigmatization or socioeconomic and racial profiling.[11,42] Most tools can be administered in minutes, such as the Smith et al[44] single-question screening for both alcohol and drug use, and the Current Opioid Misuse Measure,[45] both of which are available online. Several validated tools and where they can be obtained online are listed in the appendix.

Substance Abuse History and Assessment

Once substance abuse is identified, a thorough history of substance use should be taken, including tobacco, alcohol, and prescription drugs.[3,41] Details should include the name of the drug, route of administration, frequency, and length of time the woman has been using it. The provider should inquire about any symptoms that occur when the drug is discontinued or unavailable to determine whether physiologic symptoms of opioid tolerance and/or withdrawal exist. A similar history should be obtained for the woman's spouse, partner, or close family members.[3,41]

Table 3. Sample Protocol for Urine Drug Screening

1. Screen all pregnant women on initial visit for psychological disorders, including drug and alcohol use with corresponding verbal and/or written screening tool(s).
2. If verbal or written screen is positive for illicit or prescriptive drug use, discuss the consequences and implications of opioid use in pregnancy and UDSs with the woman.
3. Obtain informed consent for UDS.
4. Obtain urine sample and send for drug screening.
5. Review results with the woman.
6. A positive UDS may require follow-up testing.
7. A false positive should be confirmed and discussed with the woman.

Abbreviations: UDS, urine drug screen.
Sources: Sutter et al,[45] Heit et al.[46]

Urine Drug Screens

Routine urine drug screening is controversial. Because it discourages women with substance use disorders to seek prenatal care and fails to identify women with sporadic but clinically significant abuse, routine urine testing should be avoided.[3] The American College of Obstetricians and Gynecologists recommends urine drug testing only when necessary to detect or confirm suspected use.[43] If the screening for substance abuse is positive and has been discussed with the woman, the next step is to obtain consent for urine drug screening. The process for initiating testing is outlined in Table 3. Urine drug screening should only be performed with the patient's consent and in compliance with state laws.[43] Pregnant women should also be informed of the potential consequences of a positive screen, because many jurisdictions have mandatory reporting requirements.[43] The clinic guideline for chain of custody urine drug screening needs to be both simple and secure and requires standardized collection procedures that minimize error.[46] One of the difficulties with biologic screening is the potential for a false-positive result. Studies of point-of-service false-positive drug screens vary on the frequency of occurrence (2.5%-21.5%) because a number of variables can potentially influence the results.[3,8,11,46] Any potentially false readings should be confirmed with gas chromatography-mass spectrometry (GC-MS).[46] However, costs for follow-up laboratory work to verify positives or negatives may be significant and a barrier to further evaluation. The false-positive result also tends to strain the patient-provider relationship.[46] Transparency in dialogue with each patient, avoidance of labeling, and sensitivity to possible trust issues should always be considered.

Physical and Psychological Assessment

Women with OUD often have poor general health prior to and during pregnancy, including poor nutrition, weight gain, and negligent dental health.[3] If the woman is injecting heroin or prescription drugs, track marks, lesions, or abscesses may be visible on physical examination. Intoxication, sedation, erratic behavior, or withdrawal symptoms may also be present (see

section on withdrawal). Laboratory tests for sexually transmitted infections, HIV, and hepatitis B and C, as well as liver function tests, should be performed.[3,43] Tobacco use is also common. Providers should encourage cessation and provide assistance to women to quit or reduce smoking if at all possible.[3] If dental health is poor, referral to a hygienist and dentist is warranted. Constipation is a frequent problem in pregnancy in general and with opioid use in particular. Clinicians should inquire about constipation and offer advice on bowel hygiene and stool softeners as needed.[3]

A psychological evaluation should also be completed to determine whether any psychosis, cognitive impairment, dementia, and/or homicidal or suicidal ideations are present.[4] If the services of a mental health professional are available, the woman should be referred for evaluation and comanagement as needed. In the event that a timely referral is not possible, the prenatal care provider may alternatively utilize self-administered assessment tools, such as the Patient Health Questionnaire and the Mood Disorder Questionnaire for screening purposes.[3] If a woman screens positive, consultation with and/or referral to an appropriate mental health professional is warranted.

Education and Counseling

Once opioid use is identified, the provider should educate the woman as to the effects of opioids on both herself and her fetus.[3,10,41] It is important the woman understand that detoxification and abstinence-based recovery is not recommended during pregnancy because of the risks to the fetus from repeated cycles of withdrawal and the high probability of relapse.[9,41,42] Providers who are managing women with OUD in primary care settings should coordinate care with social services as soon as possible.[3,11] If professional counseling services are available, the woman and her family should also be referred in a timely manner, with continuing follow-up by the primary care provider.[41]

Antenatal Testing

There is a lack of research on antenatal testing for women with OUD. Therefore, experts in the field recommend that antenatal testing be initiated on an as-needed basis or in the presence of comorbidities, such as preeclampsia, fetal growth restriction, or preterm labor.[9] It is important to recognize that nonstress test patterns are less likely to be reactive within 4 to 6 hours of methadone maintenance administration. Similarly, biophysical profiles may be nonreassuring. Ideally, antenatal testing should be performed prior to a scheduled maintenance dose.[9]

PHARMACOLOGIC TREATMENT

Maintenance therapy with methadone remains the standard of care for heroin and nonheroin opioid addiction in pregnancy.[3,8,9,43] The rationale for opioid-assisted therapy during pregnancy is to prevent cycles of relapse and subsequent withdrawal, to discourage illicit opioid use, and to decrease the dangerous activities associated with drug use, such as needle sharing and criminal activity.[10,41,43] NAS is an expected consequence of this treatment.[10,41,43,45] More recently, research has shown that buprenorphine may have some advantages over methadone for opioid-assisted therapy, including a lower risk of overdose, decreased NAS severity, fewer drug interactions, and ability to manage treatment in an office setting and avoid daily methadone treatment center visits.[3,9,10,41,43] The following sections provide detailed information on factors to consider when deciding the most appropriate drug to recommend or use.

Methadone

Methadone maintenance treatment has been a mainstay of pharmacologic treatment of OUD since the 1970s.[9] When used for the treatment of OUD, methadone is federally mandated to be dispensed by approved methadone treatment centers.[3,43] Unless they are employed by these programs, most prenatal care providers will not be involved in initiating or dispensing methadone for opioid-assisted therapy. However, if they are providing prenatal care for women in these programs, clinicians should be aware of the treatment guidelines for methadone, monitor the woman for any adverse reactions or changes, and coordinate health care services with the methadone treatment center.[3,10,41]

Usual therapeutic doses for methadone in pregnancy range from 60 to 100 mg daily, and 20 mg daily is a typical starting dose (Table 4). Dosages are typically scheduled every 24 hours in the morning and increased every 3 to 5 days in the outpatient setting, although inpatient initiation is usually more rapidly advanced.[9] As pregnancy progresses, dosage is adjusted to avoid withdrawal symptoms. Usually, dosage adjustments will need to be made in the third trimester as the placental barrier becomes more permeable.[47] Some women may benefit from twice-a-day dosing depending on their metabolism of methadone. Dosing adjustments are guided by the presence of withdrawal symptoms prior to the next scheduled dose.[6] Of note, methadone can prolong the QT interval, resulting in torsades de pointes. An ECG is required prior to initiation of this drug.[9]

Buprenorphine

Recent and ongoing research is revealing both maternal and neonatal advantages to buprenorphine treatment in opioid replacement therapy. Buprenorphine is gradually becoming a first-line treatment over methadone as availability increases.[10,41] However, a few small studies have found that women on methadone may be less likely to relapse than women using buprenorphine.[48,49] The higher cost of buprenorphine is also a consideration, although recently, some third-party payers have begun to cover buprenorphine treatment.[50]

Until recently, buprenorphine prescribing in the United States was restricted to physicians who had participated in special training and received a license from the Drug Enforcement Agency to prescribe it.[3] In November 2016, however, passage of the CARA enabled NPs and PAs to undergo specialized training and to prescribe buprenorphine treatment in concordance with state regulations.[12,13] CNMs are not presently included in this legislation. These regulations are

Table 4. Medications for Opioid-Assisted Therapy During Pregnancy

Drug Characteristics	Methadone	Buprenorphine
Starting dose, mg	10-30	2
Target dose, mg	90	8-16
Interval at which dose may be increased	3 days	Daily
Contraindications	Opioid allergy, severe asthma, bowel obstruction (paralytic ileus)	Opioid allergy, severe asthma, bowel obstruction (paralytic ileus)
Precautions	Cardiac arrhythmias, long QT interval, concomitant SSRI therapy	Caution with CYP3A4 inducers (carbamazepine, phenobarbital), arrhythmias, CNS depression
Common side effects	Respiratory depression, withdrawal symptoms, dizziness, drowsiness, nausea, vomiting, constipation, increased sweating	Respiratory depression, withdrawal symptoms, chills, fever, dizziness, nausea, anxiety, abdominal pain, constipation, lower back pain, stuffy nose, pruritus, headache, sweating

Abbreviations: CNS, central nervous system; SSRI, selective serotonin reuptake inhibitor.
Source: Mozurkewich et al.[9]

Table 5. Providers' Clinical Support System for Medication-Assisted Therapy Training for Nurse Practitioners and Physician Assistants

	Requirements
Who is eligible?	Federal regulations allow for NPs and PAs with prescriptive authority and a DEA license, including at least Schedule III medications. State regulations may impact eligibility.
What training is involved?	Total of 24 hours required for waiver: 8 hours of PCSS-MAT training and 16 hours of one-on-one clinical practice with an approved training provider. (Details were being finalized at the time of writing.)
How many patients can be paneled with an NP or PA provider?	Total of 30 patients. After 1 year of buprenorphine management, may apply for waiver for up to 100 patients. States are allowed to change patient limit (federally mandated 30 minimum) and require additional reporting, practice setting, or education requirements.
When do these regulations expire?	October 1, 2021
Who is providing training?	AAAP in association with AANP, AAPA, ASAM, Project ECHO
Where can I get more information?	Substance Abuse and Mental Health Services Administration: https://www.samhsa.gov/ Providers' Clinical Support System for Medication Assisted Therapy: http://pcssmat.org/ American Association of Nurse Practitioners Education: NPEducation@aanp.org American Academy of Physician Assistants: https://www.aapa.org/ American Society of Addiction Medicine: http://www.asam.org/ American Academy of Addiction Psychiatry: http://www.aaap.org/ Project ECHO (Extension for Community Healthcare Outcomes) http://echo.unm.edu/

Abbreviations: AAAP, American Academy of Addiction Psychiatry; AANP, American Association of Nurse Practitioners; AAPA, American Academy of Physician Assistants; ASAM, American Society of Addiction Medicine; DEA, Drug Enforcement Agency; NP, nurse practitioner; PA, physician assistant; PCSS-MAT, Providers' Clinical Support System for Medication-Assisted Therapy; Project ECHO, Project Extension for Community Healthcare Outcomes.
Sources: PCSS-MAT,[13] SAMHSA,[51] ASAM,[52] AAAP.[53]

summarized in Table 5. However, it should be recognized that the number of licensed buprenorphine providers is currently limited. Clinicians from a variety of disciplines who care for pregnant women will need to work closely with buprenorphine prescribers. Subsequently, clinicians need to understand the usual treatment guidelines and to work closely with the prescriber in terms of overall care management and consult with more experienced physicians and specialists as needed.[3,49]

Initiation and Management of Buprenorphine

No clinical guidelines have been published to date regarding initiation of buprenorphine in pregnancy. Until published guidelines are available, less experienced providers are encouraged to consult with local or regional experts as needed to ensure safe practices. It is important to obtain accurate gestational dating prior to initiating buprenorphine treatment (Leslie Hayes, MD, staff, Integrated Addictions and Psychiatric TeleECHO Clinic, oral communication, July 14,

2016). Unless otherwise contraindicated, one clinical guideline suggests that initiation may occur in the clinic if gestation is less than 22 weeks. If gestational age is 22 to 36 weeks, buprenorphine should be started in a facility with personnel able to handle a premature newborn and a pregnant woman on opioid-assisted therapy. For pregnancies greater than 36 weeks, buprenorphine should be started in a hospital, and the woman and her fetus should be monitored for several hours postinitiation. Essentially, if the woman could potentially give birth a premature newborn, initiation should occur in a facilty capable of caring for a premature newborn (Leslie Hayes, MD, staff, Integrated Addictions and Psychiatric TeleECHO Clinic, written communication, February 2, 2017).

Initiation into buprenorphine treatment begins when the patient is abstinent from other opioids long enough to enter a state of mild to moderate withdrawal symptoms.[9] The typical starting dose is 2 mg, with therapeutic doses in pregnancy ranging from 8 to 16 mg daily (Table 3). If symptoms persist 2 hours after the initial dose, an additional dose of 2 to 4 mg, up to a maximum of 16 mg in 24 hours, may be given.[9,41] Dosing increases during the course of pregnancy are approximately 3 mg daily, primarily in the third trimester.[48] The dosage is adjusted as withdrawal symptoms occur, keeping in mind that dosing requirements change as metabolic demands evolve during the pregnancy.[49]

Naloxone

Naloxone (Narcan) is used for opioid reversal. It is also in a formulation with buprenorphine for opioid maintenance therapy (Suboxone). Use of naloxone is appropriate as needed for reversing respiratory depression in opioid overdose, and it is classified (according to the former US Food and Drug Administration dosing categories) as a category B or C drug, for use in pregnancy, depending on formulation.[49] Naloxone is an antagonist to multiple opioid receptors.[22] Onset with subcutaneous and sublingual ingestion is within 2 to 5 minutes, with a duration of approximately 30 to 120 minutes after administration.[8,22] Theoretically, naloxone can precipitate withdrawal in the fetus, but no known studies have been conducted to evaluate this. Consequently, the current recommendation is to use buprenorphine monotherapy in pregnancy.[8]

ASSESSMENT AND MANAGEMENT OF WITHDRAWAL

Opioid withdrawal symptoms occur when an individual with dependency experiences a reduction in the dose or discontinues the drug.[3,43] Withdrawal may occur voluntarily if patients try to reduce their dosage or to go cold turkey and quit taking the drug. Involuntary reasons may be related to provider refusal to fill a prescription, increasing tolerance for higher doses of the drug, or inability to obtain illicit prescription opioids or heroin.[49] Symptoms of withdrawal include increased pulse rate, sweating, restlessness, increased pupil size, bone or joint aches, gastrointestinal (GI) upset, tremor, yawning, anxiety or irritability, runny nose, and piloerection.[54] Women who use heroin may experience withdrawal in as few as 4 to 6 hours if severe addiction is present.[43] One of the challenges in assessing opioid withdrawal is that the symptoms are similar to severe influenza infection.[54] Information regarding the time since last opioid use and the presence of respiratory symptoms may be helpful in distinguishing influenza from opioid withdrawal. The Clinical Opiate Withdrawal Scale (COWS) is an excellent tool for rating opioid withdrawal symptoms in both inpatient and outpatient settings.[55] This 11-item scale assigns a numerical score to each category of symptoms. The categories are totaled to produce a sum score that indicates mild to severe withdrawal. Measurements monitor these symptoms over time to assist in determining the severity or stage of withdrawal. Symptoms are both currently and reflectively scored over the last 30 minutes.

Should withdrawal symptoms present in the absence of opioid or opioid replacement therapy, medications to use in the interim for withdrawal symptoms are available primarily over the counter. These include acetaminophen for musculoskeletal aches, loperamide for diarrhea, antacids for indigestion/GI upset, and hydroxyzine (prescriptive) or diphenhydramine for restlessness and anxiety.[41] However, there are no significant data to suggest that these medications reduce potential fetal harm in OUD.[41]

A practice that includes the care of women with OUD should prepare their front-office and clinical staff to manage women who present to the clinic with withdrawal symptoms.[3] Often, these patients are highly anxious. It is important to remain calm and avoid labeling the patient as drug seeking.[3] The patient should be assessed using the COWS tool, and a urine drug screen should be obtained to monitor appropriate use of medication and any illicit drugs. Opioid replacement dosing requirements change as metabolic demands evolve during the course of the pregnancy, requiring a dosage increase as needed.[9,41] Consultation with a specialist in opioid-assisted therapy may be needed to control the woman's symptoms.[41,49]

CARE DURING LABOR AND BIRTH

During labor and birth, women who receive opioid-assisted therapy have a need for pain management, because maintenance dosage does not provide adequate analgesia. Current recommendations are to continue the maintenance dose of methadone or buprenorphine as prescribed and supplement with opioid medications as needed to control pain.[3,9] Women in labor should be given sufficient medication to relieve pain and to avoid withdrawal. Higher doses of opioids are usually necessary to control pain, because women with long-term exposure to opioids have increased tolerance and pain sensitivity.[41,43] Intravenous opioid choices are limited to pure opioid agonists, such as morphine. Narcotic agonist-antagonist medications (eg, butorphanol [Stadol], nalbuphine [Nubain], pentazocine [Talwin]) can precipitate acute withdrawal and are contraindicated. Dosing of intravenous morphine should be individualized, proceeding cautiously to prevent sedation and/or respiratory depression.[41] Epidural and/or spinal analgesia are often good choices if the patient desires this method of pain control.[41,43]

Midwives caring for women with OUD in labor are advised to consult with a physician regarding medication management and refer for medical management as needed. It is not uncommon for women with substance use disorders to present in labor without prenatal care; therefore,

midwives should be knowledgeable about, and adhere to, institutional guidelines when caring for this group of women. In the event that a cesarean birth is necessary, neuraxial anesthesia is preferable to general anesthesia.[3,41] Safe administration of neuraxial anesthesia, however, requires that the woman be sufficiently alert and cooperative to maintain an adequate airway. Because airway compromise is common with chronic opioid or other illicit substance abuse, general anesthesia may be the only option.[41] For postcesarean pain control, injectable nonsteroidal anti-inflammatory drugs, such as ketorolac (Toradol), are usually effective.[41,49] Ketorolac may be used in conjunction with spinal or epidural morphine (Roxanol) and acetaminophen. If patient-controlled analgesia is used for breakthrough pain, it should be by demand only. The woman should be carefully monitored for respiratory depression.[41,49]

POSTPARTUM CARE AND CONTRACEPTION

In the immediate postpartum period, women should be closely monitored for oversedation, and dosages should be titrated, as needed.[41,49] Although increases may be needed in pregnancy, research has shown that methadone dosage does not often need to be reduced postpartum.[41] Because buprenorphine does not usually require large dosage adjustments in pregnancy, the same dose may also be sufficient in the postpartum period.[41] Women should be screened routinely for postpartum depression and counseled carefully about contraception. Because women with OUD have high rates of unintended pregnancy (85%), contraceptive counseling is vital.[54] Ideally, long-acting reversible methods should be available prior to hospital discharge if the woman desires one of these methods of contraception.[3,41,49] Hospital discharge should be coordinated so that the woman can obtain either methadone or buprenorphine without an interruption in treatment.[3,41,49] Access to psychosocial services, nurse home visiting, and addiction medicine specialists is important for long-term recovery. In general, experts recommend that opioid-assisted therapy should continue until the woman is in a stable life situation with support to prevent relapse.[3,41,49]

NEONATAL ABSTINENCE SYNDROME

NAS is an expected and treatable condition following fetal exposure to opioid agonists.[41,56] The opioid abuse epidemic has increased rates of NAS from 1.20/1000 births (in the year 2000) to 3.39/1000 births (in 2009), with an overall increase of 383% between 2000 and 2012.[46,57] NAS is a cluster of symptoms that include excessive crying, decreased postprandial sleep periods resulting in poor-quality sleep, poor feeding attributed to uncoordinated sucking reflex, and observed generalized seizure as a result of opioid withdrawal beginning at birth.[46,58]

The modified Finnegan Neonatal Abstinence Scoring System is used to assess the degree of NAS.[58] Beginning at birth, newborns are scored at 3-hour intervals, with assessments representing the symptomology displayed over the past hour. It is recommended that the same caregiver perform the assessments to improve accuracy.[44] Although the frequency of seizures in NAS is low, the maternal use of opioids and the presence of neonatal seizures is diagnostic for neonatal opioid withdrawal.[45]

NAS typically affects the GI system, central nervous system, and the autonomic nervous system.[45] Women should be counseled about what to expect as their newborn recovers from NAS. Newborns exposed to maternal methadone may have withdrawal symptoms from 72 hours after birth to 2 weeks postpartum.[59] In general, newborns exposed to maternal buprenorphine have a shorter course of symptoms, which develop from 12 to 48 hours after birth and last up to 96 hours postpartum. Symptoms may persist up to 7 days before resolution.[9] Although opioid monotherapy is recommended,[45] insufficient evidence is available to demonstrate the best management for these patients. A pediatric specialist with training and experience in NAS should provide hospital care and initial follow-up until the newborn is stable and gaining weight.[59]

BREASTFEEDING

Although small amounts of methadone and buprenorphine are present in breast milk, the general consensus is that breastfeeding should be encouraged in women who are not HIV-positive or using additional drugs.[3,41,49] In general, neonatal withdrawal severity has been noted to be significantly lower in newborns breast fed while the mother was on methadone, buprenorphine, or prescribed opioids compared with formula-fed newborns.[32] When they occur, withdrawal symptoms may be delayed in breast-fed versus formula-fed newborns. Breastfeeding is therefore recommended unless other contraindications exist.[59]

ETHICS IN MANAGEMENT AND TREATMENT

In a number of states, a positive urine drug screen in a newborn is considered evidence of child abuse.[60] Recent federal legislation requires that all children under 3 years who are substantiated as child maltreatment victims be referred to child protection services.[61] However, state, tribal, and local agency policy varies widely.[61] It is therefore advised that clinicians stay abreast of local policy regarding this issue. Although there is a higher incidence of child abuse in women with substance abuse disorder, it is important to recognize that not all parents who use drugs abuse their children.[30] Often, a vulnerable family situation may be subject to significant additional stress as a result of contacting authorities. Parents should be referred to local services offering parenting classes, home visitation programs, and for treatment of disorders such as anxiety, depression, and posttraumatic stress disorder.[3] Continuity of care is helpful for monitoring the health of the woman, her child, and her family. Relapse is common in women with OUD, as is unplanned pregnancy; therefore, close follow-up and coordination of support services are important aspects of long-term recovery.[3,41]

DISCUSSION

Opioid abuse and addiction are at crisis levels in the United States.[57] Many pregnant women do not have access to opioid replacement therapy. With the expansion of specifically trained primary care clinicians providing buprenorphine

opioid replacement therapy in 2017, greater access to treatment will be available. This not only reduces the time spent by the woman on treatment by reducing daily visits to a methadone treatment center, but it also lessens some of the stigma associated with opioid replacement therapy by placing treatment in a familiar, primary care setting. The provider will be more familiar with the woman and her family and support system and will be able to engage services that may be better matched to the woman's needs. However, challenges will remain for monitoring diversion or illicit drug use, regardless of how the opioid replacement therapy is delivered. Diligence with methodical evaluation and follow-up will minimize these possibilities within the primary care setting and will provide a more focused, patient-friendly therapeutic environment. Both women and their children will benefit from the increased access to opioid replacement therapy.

CONCLUSION

Opioid use disorder in pregnancy is a challenge to patients, clinicians, and communities. With the recent changes in legislation, a broader spectrum of clinicians will gain prescriptive privileges for opioid replacement therapy, thereby increasing access to care for pregnant women with OUD. The greatest challenges will be in training both experienced and new clinicians in opioid replacement therapy, developing community resources for support, and sustaining provider practices to provide treatment. Only through concerted efforts to bridge the gap in appropriate resources and clinician training can we as a society begin to address this critical and multifaceted issue.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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Appendix: Opioid Use Disorder Resources

Name of Resource	Brief description	Link
American Society of Addiction Medicine National Practice Guideline	Guidelines for the use of medications in the treatment of addiction involving opioid use	http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24
COWS	Clinical Opioid Withdrawal Scale to assess level of opioid withdrawal	https://www.drugabuse.gov/sites/default/files/files/ClinicalOpiateWithdrawalScale.pdf
CRAFFT	Risky substance use screen tool (≤ 21 years old; multiple language)	http://www.ceasar-boston.org/CRAFFT/screenCRAFFT.php
Drug Abuse Screening Test-10	Brief drug use screening tool (Adult version)	https://www.drugabuse.gov/sites/default/files/dast-10.pdf
Drug Abuse Screening Test-20	Brief drug use screen screening tool (Adolescent version)	http://www.emcdda.europa.eu/html.cfm/index3618EN.html
GAD-7	Generalized anxiety disorder screening tool	https://psychology-tools.com/gad-7/ http://www.mdcalc.com/gad-7-general-anxiety-disorder-7/
NIDA Drug Use Screening Tool	Quick, risky substance use adult screening tool	https://www.drugabuse.gov/nmassist/
Patient Health Questionnaire	Depression screening tool	https://www.drugabuse.gov/sites/default/files/files/PatientHealthQuestionnaire9.pdf
Tool resources	US government opioid and pain management tools website	https://www.drugabuse.gov/nidamed-medical-health-professionals/tool-resources-your-practice/screening-assessment-drug-testing-resources/chart-evidence-based-screening-tools-adults
Urine Drug Testing in Clinical Practice	Patient-centric guidelines for use with point of service urine drug testing	http://www.remitigate.com/wp-content/uploads/2015/11/Urine-Drug-Testing-in-Clinical-Practice-Ed6_2015-08.pdf