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Substance use disorders in pregnancy: clinical, ethical, and research imperatives of the opioid epidemic: a report of a joint workshop of the Society for Maternal-Fetal Medicine, American College of Obstetricians and Gynecologists, and American Society of Addiction Medicine

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Although perinatal substance use disorders, particularly those that involve opioids, have become a major public health issue in the United States, comprehensive, evidence-based guidance for the prevention and management of these disorders during pregnancy is lacking. Leaders in obstetric care, addiction medicine, mental health, and pediatrics gathered for a 2-day workshop, "Substance Use Disorders in Pregnancy," that was held in conjunction with the Society for Maternal-Fetal Medicine's 38th Annual Pregnancy Meeting. Given what has recently been termed an *opioid epidemic*, much of the workshop centered on identification and management of opioid use disorder (OUD) that included appropriate strategies to limit both opioid use and OUD. Goals of the workshop were to discuss critical issues that pertain to perinatal substance use disorders, with a focus on OUD in particular; to draft preliminary recommendations regarding screening, pain management, and medication-assisted therapy (MAT) for OUD during pregnancy; and to delineate research gaps.

Epidemiology of opioid use in pregnancy

Epidemiologic evidence that was presented at the workshop demonstrated that rates of substance use in pregnancy have increased significantly in the past decade and that rates of OUD in pregnant and postpartum women have increased in parallel:

- One study reported that 21.6% of pregnant women enrolled in Medicaid receive a prescription for opioids.[1]
- From 2000–2009, antepartum maternal opiate use increased from 1.19 (95% confidence interval (CI), 1.01–1.35) to 5.63 (95% CI, 4.40–6.71) per 1000 hospital births per year.[2]
- In 1 study, 85.4% of women filled an opioid prescription after a cesarean delivery. The average number of pills dispensed was 40; the median number of pills consumed was 20; and the average number of leftover pills was 15. Most women (95.3%) did not dispose of their leftover medications.[3]
- One study reported that 4.7% of pregnant women reported using an illicit substance in the past month.[4]
- One study reported that 1 in 300 women will become dependent on opioids after a cesarean delivery.[5]
- The incidence of neonatal opioid withdrawal syndrome (NOWS)* has increased; the cost of NOWS treatment in the United States reached approximately $1.5 billion in 2015.[6]
- Substance use plays a role in pregnancy-associated deaths (deaths of women while pregnant or within 365 days of pregnancy from any cause related to or aggravated by pregnancy). In Texas, Maryland, and Alaska, 17%, 15%, and 22% of pregnancy-associated deaths, respectively, were attributed to substance use.[7–9]

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*The term *neonatal abstinence syndrome* has also been used for this condition; however, it is a general term that refers to neonatal withdrawal from other types of substances in addition to opioids.

Workshop structure and key findings

Following presentations on epidemiology, prenatal screening, pain management, and treatment modalities of OUD in pregnancy, workshop participants were assigned to 1 of 3 breakout groups to discuss the following key issues in greater depth and to make preliminary recommendations: (1) screening and testing for substance use disorder, including OUD, in pregnancy; (2) pain management during the antepartum, intrapartum, and postpartum periods; and (3) management modalities for pregnant women with OUD.

The following key findings emerged from the workshop discussions:

- All pregnant women should be screened for substance use at the first prenatal visit with the use of a validated questionnaire, such as the National Institute on Drug Abuse (NIDA) Quick Screen Tool.
- Biologic testing, when performed, should be undertaken only with the woman's informed consent and when its benefits outweigh any potential harms, which include those related to mandatory state reporting laws.
- For opioid-naïve women, nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, unless contraindicated, should be given as first-line treatments for pain after a routine vaginal birth. A short course of low-dose opioids can be considered for severe pain that is not managed effectively by nonopioid options. Severe pain after vaginal delivery is unusual and should prompt an evaluation for unrecognized complications.
- For opioid-naïve women, NSAIDs and acetaminophen, unless contraindicated, should be given as first-line treatments for pain after cesarean delivery. The addition of opioids to the pain management regimen should be considered if pain persists.
- On discharge from the hospital, if an opioid-naïve woman requires opioids for persistent pain, she should be counseled about the benefits and risks of opioids, side-effects, and potential for misuse; a limited number of opioid pills should be prescribed.
- All pregnant women with OUD should be offered maintenance therapy with methadone or buprenorphine. The choice of agent and dosages for therapeutic maintenance should be made with the use of an individualized, patient-centered approach that is based on the disease model of substance use disorder.
- Although the US Food and Drug Administration (FDA) has approved naltrexone for the treatment of OUD, data are insufficient to support the initiation of naltrexone therapy during pregnancy. Naltrexone may be continued for those patients who already are taking this medication and who become pregnant after a careful assessment and communication of the risks of discontinuing naltrexone (eg, risk of relapse) and the limitations of data surrounding its use in pregnancy.
- Pain management for women who are taking opioids for chronic pain or who have OUD during pregnancy and during and after delivery involves a multidisciplinary approach that may include an anesthesia consultation. Neuraxial analgesia during labor should be encouraged. Postpartum pain should be managed with the use of a multimodal approach that starts with nonopioid pain relief. If pain persists for >24 hours, a full opioid agonist (eg, fentanyl or hydromorphone) may be ordered.
- Although MAT for women with OUD is considered the standard of care, some women may prefer or be motivated to undergo medication-assisted withdrawal during pregnancy. This option should be undertaken only with careful patient selection, close supervision, and appropriate behavioral and social support resources that extend into the postpartum period.
- Management of OUD during pregnancy requires an approach that involves a wide range of health-care, social, and behavioral services to address the complex needs of this patient population. Two models of care that have been proposed are a collaborative care model and a "1-stop shop" model; both models have unique advantages and disadvantages.

Workshop participants acknowledged that significant research gaps in evidence to guide best-practice care of this population remain. Each of the following sections also includes suggested areas that require future research. It is hoped that this workshop will provide the first step toward the development of comprehensive, evidence-based guidelines that focus on the unique needs of pregnant and postpartum women with OUD and will create an opportunity for education that dispels myths surrounding care and management and leads to the creation of validated and workable solutions for this population.

Screening and testing for substance abuse, including opioid use, in pregnancy

Definitions: screening vs testing

Screening is used on a population level to determine who is at high risk for a disease. Ideally, it should take place only when interventions are available to prevent or treat the disease state. Screening is efficient if the background prevalence of the disease state warrants screening. Given that substance use in pregnancy is common, that the consequences of substance misuse are substantial, and that treatment interventions are available, screening pregnant women for drug and alcohol use is warranted.

Screening tests should be easily administered, acceptable to patients, and economical. In this report, we refer to screening as a universally administered questionnaire designed to ascertain who is at high risk for having a substance use disorder in pregnancy. Biologic testing of urine, blood, or hair is discussed as a test and not as a screening technique. A biologic test may be useful only in selected situations. Universal biologic testing to screen pregnant women is not recommended.

When and whom to screen for substance use disorder

Ideally, screening for substance use disorder should occur when clinicians in a health-care system first recognize a pregnancy. In most cases, this would be the first prenatal visit. However, emergency rooms, primary care offices, and urgent care centers are all places where pregnancies are diagnosed. Clinicians can facilitate early substance use disorder treatment by considering the use of a basic screening questionnaire coupled with a list of treatment options in any setting in which a woman may be newly diagnosed. Screening should be implemented with every pregnant woman, regardless of whether the provider has suspicions of substance use. The goal of screening is to identify those women with substance use disorders and to help all such women receive treatment if needed; many women with substance use disorder will be missed if screening is based only on provider suspicions. Further, provider suspicions are subject to conscious and unconscious biases that may both overburden some groups and leave other groups undiagnosed. If, separate from universal screening, objective clinical findings or reported history increase a provider's concern during pregnancy or the postpartum period, repeat screening at that time or consideration for testing is warranted. Indeed, in situations in which a provider has specific concerns about an individual patient, biologic testing may be a better choice (eg, an obtunded patient), although this should be undertaken, as discussed later, only with the patient's consent with the goal of providing comprehensive care.

Types of screening tests

The American College of Obstetricians and Gynecologists (ACOG) advocates the administration of a brief substance use screening questionnaire to all pregnant women that would trigger a brief behavioral intervention and referral, if warranted.[10,11] Among the advantages of such brief self-reports are that they can provide longitudinal information about the use of a variety of substances over time and provide a broader window of detection than biologic tests, for which detection may be limited by the half-life of substance metabolites in tested tissue. Given the short window of detection for some substances (eg, cocaine or alcohol), self-report can identify active use among persons whose toxicology test results are negative. However, there are several limitations with questionnaire-based screening. Health-care professionals may be hesitant to inquire about substance use or misuse because of perceptions that patients will be "insulted" if asked about substance use; clinicians may also have limited time to screen, advise, and refer patients.[12] Additionally, underreporting of substance use by patients is common,[13] particularly during pregnancy.[14–17] Indeed, women have many reasons to be reluctant to disclose substance use in pregnancy. They may worry about legal sanctions and child custody issues as well as the stigma of being a mother who uses substances. Such fears can discourage them from seeking prenatal care altogether.[12,18,19]

An additional issue in considering screening instruments for substance use disorders is that the validity, reliability, and clinical utility of standardized questionnaires that are used in screening for illicit drug use have received only limited evaluation in pregnancy.[20] Many tools that are used outside of pregnancy attempt to identify individuals with a substance use disorder. However, substances that are used in pregnancy may be prescribed or recommended for recognized and appropriate medical indications; thus, their use does not qualify as disordered.[21] Furthermore, screening may not indicate active use because many women attempt to temporarily limit or curtail their use during pregnancy.[22] Accordingly, indicators of actual use are more appropriate as a screen for substance use in pregnancy, although past use is a risk for current use.

Although screening measures for alcohol use or abuse in pregnancy have received the greatest attention, screeners for illicit drug use or prescription drug misuse or for broad measures of substance use are far less developed. At least 6 measures have been assessed for overall screening of substance use in pregnancy, and further evaluation of their utility in the identification of the use of opioids in pregnancy is ongoing. An explanation of these 6 measures is provided below.

Drug abuse screening test

The Drug Abuse Screening Test (DAST-10) is a 10-item general substance use screening questionnaire.[23] It has been evaluated by comparing its results with results of biologic testing of urine and hair samples that were obtained from a sample of 300 low-income, postpartum women.[17] Twenty-four percent of the sample scored positive on the DAST but had negative toxicology results, whereas 19% of the sample had positive toxicology results but denied drug use on the DAST. Measures of merit of the DAST-10 (with the cutoff score of 1) for any drug use showed a sensitivity of 47%, specificity of 82%, positive predictive value of 43%, and negative predictive value of 84%.[17] Given these metrics, the clinical utility of the DAST-10 as a screening instrument is not strong, although it may be suited for the detection of substance use disorders rather than use in pregnancy. An additional limitation is that, with 10 questions, many may find it too lengthy.

4Ps screen

The 4Ps screen was first developed by Hope Ewing in 1990.[24] Since then, the measure has evolved along 2 paths. The first path is the 4Ps Plus (NTI Publishing), which includes 5 questions, is copyrighted, and only available for a fee. The utility of this screening tool was reported in a study of 228 pregnant women.[25] Compared with results from a clinical interview, the 4Ps Plus correctly identified the status of participants as using or not using substances 78% of the time. The sensitivity was 87%; specificity was

76%; positive predictive value was 36%, and negative predictive value was 97%.[25] The instrument has not been validated against biologic measures. The second path for development of this screener has been the 5Ps Prenatal Substance Abuse Screen for Alcohol and Drugs, as adapted by the Massachusetts Institute for Health and Recovery,[26] and is available for use without a fee. The wording of questions is slightly different from the 4Ps Plus, but it conveys similar content. Although at present in wide use in Massachusetts, California, Maine, Virginia, and South Carolina, the 5Ps has not been subject to rigorous, systematic study (eg, comparison with a criterion standard, calculation of measures of merit). The 4Ps Plus screening questions are as follows:

(1) **P**arents: Did either of your parents have a problem with alcohol or drug use?

(2) **P**eers: Do you any of your friends have a problem with alcohol or other drug use?

(3) **P**artner: Does your partner have a problem with alcohol or drugs?

(4) **P**ast: Have you ever drunk alcohol?

(5) **P**regnancy: In the month before you knew you were pregnant: How many cigarettes did you smoke? How much wine/beer/liquor did you drink? How much marijuana did you smoke? How much medication for pain, anxiety, or depression, such as Vicodin, Valium, or Oxycontin, did you take? (© NTI Upstream, 2008. Reprinted with permission of the publisher. May not be copied or reproduced without express written consent of NTI Upstream. www.ntiupstream.com.)

Substance use risk profile-pregnancy

The Substance Use Risk Profile-Pregnancy includes 3 questions: (1) Have you ever smoked marijuana? (2) In the month before you knew you were pregnant, how many beers, how much wine, or how much liquor did you drink? (3) Have you ever believed that you needed to cut down on your drug (including the nonmedical use of prescription medications) or alcohol use?

Individuals are classified into low (score=0), moderate (score=1), or high risk (score=2).[27] More than 1 alcoholic drink equals 1 point, as does any "yes" answer.

The 3-question Substance Use Risk Profile-Pregnancy was developed in a training sample of 1610 pregnant women and cross-validated in a separate validation sample of 1704 pregnant women. In this evaluation, it identified alcohol use with a sensitivity of 48% and specificity of 85% and identified marijuana use with a sensitivity of 68% and specificity of 86%.[27]

CRAFFT screening tool

The CRAFFT Screening Tool for Adolescent Substance Abuse was designed for screening in adolescents.[28] It includes 6 "yes/no" questions, with each "yes" scoring 1 point. A score of $\geq$2 is generally considered to be a positive screening test result. The CRAFFT questions are as follows:

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

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

A—Do you ever use alcohol or drugs while you are by yourself, alone?

F—Do you ever forget things that you did while using alcohol or drugs?

F—Does your family or friends ever tell you that you should cut down on your drinking or drug use?

T—Have you ever gotten into trouble while you were using alcohol or drugs?

Although developed for screening of adolescents, the CRAFFT has been preliminarily tested in in small pilot study of young pregnant women as well (n=30).[29] With the use of calendar-based recall as the standard, CRAFFT had a positive predictive value of 90% and a negative predictive value of 80%. Compared with a standard elicited from a diagnostic interview, the positive predictive value was 58% and the negative predictive value was 83%.[29]

Wayne Indirect Drug Use Screener

The Wayne Indirect Drug Use Screener includes 6 "true/false" items and was developed specifically for use in perinatal populations[30]:

(1) I am currently married.

(2) In the past year, I have been bothered by pain in my teeth or mouth.

(3) I have smoked at least 100 cigarettes in my entire life.

(4) Most of my friends smoke cigarettes.

(5) There have been times in my life, for at least 2 weeks straight, where I felt like everything was an effort.

(6) I get mad easily and feel a need to blow off some steam.

In a validation study, the sensitivity of the Wayne Indirect Drug Use Screener was 76%, and specificity was 68%. In this study, the instrument was found to outperform the DAST-10, and scores showed a strong linear association with toxicology results.[30]

NIDA Quick Screen

The NIDA Quick Screen[31] has been recommended by NIDA for use in primary care settings and only recently has been evaluated in pregnant women.[32] It is a simple instrument that includes 4 questions that ask directly about the frequency of

substance use, with response options being "never," "once or twice," "monthly," "weekly," "daily," or "almost daily":

In the past year, how often have you:

(1) had ≥4 drinks a day?

(2) used tobacco products?

(3) used prescription drugs for nonmedical reasons?

(4) used illegal drugs?

Although the component questions of the NIDA Quick Screen have been validated separately for the identification of the use of individual substances, the package of 4 questions has not yet been examined as a whole for pregnancy screening.[33–35]

Preferred Tools and Future Research

Many questions remain for future research and evaluation of screening tools for substance use disorders in pregnancy, including which screening instrument is most effective and whether implementation of universal screening will improve outcomes. Until further study indicates that 1 of these 6 tests or another screening test for substance use disorder is clearly superior to the others, the public availability and ease of use of the NIDA Quick Screen, 4Ps, and CRAFFT argue for their preference. In the meantime, integration of substance use screening in prenatal care is a logical first step toward the identification of substance use and reduction of harmful effects for mothers and babies.

Interventions after a positive screening test result

When a pregnant woman is identified by screening to be at high risk for a substance use disorder, follow-up evaluation is required. Follow-up starts with a conversation that reviews the results of the screening tool, risk factors, and history of substance use and asks the patient about active use of individual substances and the frequency of their use. It is critical that, in these discussions, the provider maintains a nonjudgmental approach, much as one would do when informing a patient of an abnormal glucose screening test result. Terms such as "addict" should be avoided, and the provider should engage the woman as someone interested in offering care and treatment for a clinical condition, not as someone seeking to scold or punish. The woman should be offered information about the effects of substance use during pregnancy on both herself and her fetus and about local resources for evaluation and treatment of substance use disorder.

Before following up initial screening with further conversations and counseling, however, it is important for the provider to understand the local laws and culture that surround substance abuse in pregnancy and counsel the woman on these issues so that they together consider the consequences of affirming present or past problems of substance abuse. For example, in addition to conveying the benefits of diagnosis and treatment for a women's health and the health of her pregnancy, the provider should discuss when and if reporting of results is required and what the implications of such reporting are for custody and parenting. As with screening itself, informed by such an understanding of benefits and consequences, patients may decline further questioning and conversation.

Drug treatment services linkage and referral

Women should be informed that substance use disorder is treatable and that treatment is safe and encouraged during pregnancy. Accordingly, when screening and subsequent follow-up suggest the presence of OUD, the importance of transitioning to MAT should be emphasized. Providers should have a way to facilitate a prompt referral for MAT, either with an outside provider or start buprenorphine therapy themselves. The section on "Management Modalities for Pregnant Women With OUD" gives further details about the use of MAT in pregnancy.

Care collaboration and support services

A multidisciplinary approach to clinical care and connection to psychosocial support services can improve the chances of treatment success for women with substance use disorders in general. As discussed in greater detail in subsequent sections of this report, depending on individual circumstances, some women can benefit from consultation with anesthesia or pain service providers to discuss pain management. Consultation with pediatric and neonatal intensive care providers to review neonatal care protocols for care of newborn infants who are exposed on an ongoing basis (as fetuses) to opioids also may be beneficial. Such collaborations increase preparedness for and transparency around delivery planning. Additionally, women can benefit from behavioral health referrals, services for addressing social determinants of health (eg, housing or food insecurity), and connection with peer and community supports. In the postpartum period, consideration should be given to transferring a woman's substance use management from her obstetric care providers to an identified primary care provider.

Biologic testing

A positive response to a self-report screening questionnaire or a woman's history may lead a clinician to offer a biologic test. In some cases, a decision to offer biologic testing of a pregnant woman must be informed by local legal mandates; however, in this discussion, we focus on when testing is medically appropriate. Opioid biomarkers may be assayed from blood, saliva, hair, or urine samples; breath testing is an additional option for other substances, such as alcohol.[36] The advantages of testing for biologic markers of substance use include objectivity, ability to test for multiple substances, and well-established validity.[36] However, biologic tests do not distinguish between occasional and regular use.[20] Additionally, although a

number of different matrices have been used and a variety of assays are available, there is no general agreement as to which is superior and what cutoffs should be used.[14] Furthermore, the short half-life of most substances and their related metabolites limits detection to recent use only.[37] Overall, although its sensitivity may be limited by its short window of detection, the specificity and positive predictive value of urine drug screening, a common approach, is extremely high.

Biologic testing may also be undertaken in specific medical situations. Each practice or hospital should have explicit criteria for drug testing to avoid demographic or other profiling and discrimination. If medical criteria are present, a drug test should be offered to the woman. It is important to reiterate that consent is needed to test, unless the patient is unable to consent because of loss of consciousness. In setting policy for drug testing, the following situations should be considered. Not all are specific to OUD, but many may raise concern for the use of other substances, as indicated:

- Obtunded or unconscious patient
- Patient who is falling asleep mid-sentence or shows other evidence of being intoxicated
- Patient with no prenatal care at the time of delivery
- Patient with recent physical evidence of injection use (eg, "track marks")
- Patient with unexplained soft tissue infections or endocarditis
- As part of the treatment of a patient to whom you are prescribing MAT to evaluate for any continued separate use of opioids or other substances
- At the time of delivery in a patient previously identified as having used certain illicit drugs or inappropriately used prescription medications, at any point in the pregnancy
- In patients with acute clinical complications such as placental abruption or unexplained severe hypertension (cocaine, amphetamines)

Women should be tested immediately on admission to a labor and delivery setting and not after they have been treated with any medication that could cause a positive test result. If the pediatrics team requests testing of a woman because the baby is showing signs of withdrawal, it is preferable to test the baby; the woman may test positive because of the pain medicine she may have received at delivery or postpartum.

Biologic testing panels

The constituent components of biologic drug testing panels are often determined by the hospital laboratory, based on local drug usage profiles. However, illicit drugs in the community can change rapidly; ideally, and if possible, providers should be aware of local trends. The hospital laboratory, health department, or coroner's office may help provide information about the local pattern and prevalence of substance use. Importantly, women themselves may not always be aware of what they are taking. For example, fentanyl may be sold as heroin or mixed with cocaine. Biologic drug testing panels may not include common drugs of abuse such as fentanyl, carfentanil, buprenorphine, or so-called club drugs such as Rohypnol ("roofies"), ketamine, gamma-hydroxybutyrate, MDMA (ecstasy), or inhalants.[38] If the panel does not include these substances, depending on the situation, tests for these drugs should be added separately, or the laboratory should be encouraged to add them to their standard panels.

Occasionally, a patient may reveal drug use, but the biologic drug test result may be negative. In this case, the provider should attempt to elicit as much information from the patient as possible about the drug (for example, how it is taken) and then work with the laboratory to decide which additional tests may be useful in determining the patient's exact drug usage.

False-positive and false-negative biologic testing results

Understanding the type of drug test that a laboratory is using will inform interpretation of test results. Some laboratories perform a more rapid preliminary/screening test first that is followed by a confirmation test for those samples with positive test results. Preliminary screening tests and confirmation tests often require different times to return a result. Although a preliminary result may be needed to treat a patient in an urgent situation, providers must be aware that rapid test results may not be definitive. Compared with confirmatory tests, preliminary screening tests may yield more false-positive results. Substances such as poppy seeds, pseudoephedrine, and dextromethorphan, for example, have been reported to cause false-positive results.[38] False-negative results may also occur if the sample is adulterated with another substance or if a patient provides a urine sample that is not her own. Prevention of the latter situation involves educating staff about signs that a sample is not the patient's (for example, staff should note if the sample does not seem to be at body temperature when provided by the patient). If staff members are unsure, in the case of a pregnant woman, the sample can be tested for human chorionic gonadotropin. If the human chorionic gonadotropin test result is negative in a known pregnant woman, a repeat sample should be requested. Although it is possible that drug-free urine from a pregnant woman can be purchased illegally, it is more likely that urine bought to confound the test will not be from a pregnant woman.

Arguments against universal biologic screening

There are several reasons that the use of universal biologic testing to screen for substance use disorder in general or OUD specifically is not recommended. First, as discussed earlier, biologic drug testing is not foolproof. False-negative and false-positive results can occur. Second, it also is possible that poorly timed drug tests, in

contrast to questionnaire-based screening, will fail to detect substance use or, conversely, will detect medicinal drugs used during care. Third, biologic testing is limited by substances that are included in a panel. Finally, biologic testing is generally costlier than questionnaire-based screening. For these reasons, in addition to the fact that in some states the consequences of a false-positive result can be quite severe (eg, loss of child custody or jail), it is recommended that biologic drug testing of a pregnant woman should be undertaken for medical reasons only and with her consent.

Future research

Many questions related to screening and testing for substance use disorder and OUD remain unanswered. Although several screening questionnaires are available, data are insufficient to determine which, if any, is superior. In addition, the optimal number of times to screen is unclear. Although screening carries potential risks, (for example, women may be deterred from seeking prenatal care), there is a lack of research that details and quantifies such risks. Screening can be conducted through electronic formats that provide a sense of greater confidentiality than face-to-face screening, but the performance of such screening modalities for substance use disorder and OUD in pregnancy needs to be studied. Although research into many of these questions is ongoing, continued work is required to identify best practices and develop guidelines for screening pregnant women for OUD.

Pain management during pregnancy and the postpartum period

Use of oral opioids after a vaginal or cesarean delivery contributes to the concerning rise in individuals with OUD in 2 critical ways: (1) the use of opioids exposes women to addictive medications, potentially leading to chronic use and misuse, and (2) prescribing a large number of pills can lead to leftover medications in the home that are available for diversion or misuse. Separate from concerns about misuse and diversion, opioids are also associated with a range of side effects that are not associated with alternative options for pain management that include nausea, dizziness, lethargy, and constipation. Accordingly, there is a growing consensus that pain management after delivery should be based on the use of nonpharmacologic approaches and nonopioid analgesics, with oral opioids used on an as-needed basis as rescue but not first-line medications.

Pain management after vaginal delivery among opioid-naïve women

Pain after a vaginal delivery varies by individual but is generally mild-to-moderate in severity and, in most cases, is of limited duration. Recently, Komatsu et al[39] enrolled 99 nulliparous women who had an uncomplicated vaginal delivery at 1 institution and followed their postdelivery pain scores, analgesic use, and functional recovery daily for up to 3 months. These women experienced a median of 14 days (interquartile range [IQR], 7–24) to pain resolution, 11 days (IQR 5–17) to analgesic cessation, and 0 days (IQR 0–2) to opioid cessation after delivery. Pain scores were in the mild-to-moderate range for the majority of women in the study.

Evidence-based strategies for pain management that specifically have been tested on women who had vaginal deliveries are limited, and management of acute pain in this context is largely extrapolated from other areas. Such extrapolation suggests that pain management options include analgesic and nonanalgesic medications as well as other adjunctive, nonpharmacologic approaches. Limited data exist regarding the efficacy of interventions such as ice, heat, hydrocortisone application, and local anesthetic application; however, no harms have been described in the literature to such approaches, and continued use seems reasonable. Future research should define the benefit of nonpharmacologic approaches and identify optimal analgesic regimens, with the goal of achieving a functional recovery rather than a specific pain score.

In many settings and practices, oral opioids are administered commonly during inpatient recovery and are prescribed as part of outpatient recovery after vaginal delivery. Recent data have shown that a significant proportion of opioid-naïve women receive opioids for pain management after a vaginal delivery, both during hospitalization and at discharge. A nationwide study from 2003–2015 noted that 28.5% of opioid-naïve women were dispensed opioids within 1 week of discharge, the vast majority of whom had an uncomplicated delivery.[40] The dosages that were dispensed are also much higher than a single or few doses; the median dosage of opioids dispensed was 150 morphine milligram equivalents, equal to 20 5-mg tablets of oxycodone. A single center study of women in Illinois who had a vaginal delivery noted that 25% of women had taken opioids within the last 24 hours of their hospitalization (median, 20 morphine milligram equivalents) and that 30% of women were discharged with an opioid prescription (median, 200 morphine milligram equivalents).[41,42] The latter study noted an inverse association between nonopioid analgesic use and opioid use. Because pain after vaginal delivery tends to be in the mild-to-moderate range and quickly resolves, we do not recommend the routine use of oral opioids after vaginal delivery.

Our recommendations for immediate postdelivery pain management after a vaginal delivery among opioid-naïve women include the following (in the absence of contraindications to these medications):

- Nonpharmacologic, adjunctive approaches, such as an ice pack, heating pad, hydrocortisone, and local anesthetic application to the perineum
- Acetaminophen: 975 mg every 8 hours by mouth or 650 mg every 6 hours by mouth
- Ibuprofen: 600 mg every 6 hours by mouth
- Ketorolac: 15 mg/30 mg intravenous/intramuscular every 6 hours for 48 hours if pain is not managed with

acetaminophen and ibuprofen alone or oral NSAIDs are not tolerated
- Consideration of epidural morphine or hydromorphone if there is a significant laceration repair before catheter removal (must be able to provide respiratory monitoring for 24 hours after the procedure)
- A short course of low-dose opioids (eg, 5-10 tabs of hydrocodone 5 mg) can be considered for severe pain not adequately treated by the aforementioned options. Severe pain after vaginal delivery is unusual and should prompt an evaluation for unrecognized complications.

Pain management after cesarean delivery among opioid-naïve women

Opioids are commonly prescribed at the time of discharge after cesarean delivery in the United States. A recent survey of women from 6 academic medical centers reported that 85% of women filled an opioid prescription after discharge after a cesarean delivery.[3]

Such patterns must be understood in the context of data that describe ongoing and subsequent chronic use after acute exposure. The risk of persistent opioid use after cesarean delivery was quantified in a 2016 study of 80,127 opioid-naïve women who were enrolled in a commercial insurance plan.[5] The investigators found that approximately 1 in 300 of women who were exposed to opioids after cesarean delivery went on to use them chronically in the year after discharge. The risk of persistent opioid use was markedly higher in these patients than in a control group of women who delivered vaginally and who were not exposed to opioids. Risk factors for persistent use that were identified in this analysis included younger age, smoking, use or abuse of other drugs, chronic pain conditions (that included back pain, headaches, and fibromyalgia), and use of antidepressants or benzodiazepines.

These findings highlight the need to develop and evaluate strategies that prevent the transition to chronic use and misuse after acute exposure in this setting. Potential approaches that should be studied include assessment of the impact of limiting the dosage and duration of the initial opioid prescription, maximizing the use of nonopioid analgesics, and development of systems to track medication refills to flag women who are transitioning from acute to chronic use.

Leftover medications (doses prescribed in excess of those needed to treat acute pain) have been demonstrated to be an important source of opioids that are used nonmedically.[43,44] They also create the potential for accidental exposure among children who live in the home.[45] Survey data suggest that the majority of women who fill an opioid prescription after a cesarean delivery do not use the full amount prescribed and frequently do not dispose of the leftover medication.[3,46,47] For example, 1 study found that the median number of dispensed opioid tablets after cesarean delivery was 40 (IQR, 30–40), and the median number consumed was 20 (IQR, 8–30).[3] Of the women with unused medication, 95% did not dispose of it.

Given these findings, there is a need to develop and test approaches to better align the amount of opioid medication that is prescribed with what women require. Strategies that have demonstrated promise in this regard include the use of shared decision-making (in which women select the quantity of opioids they want to be prescribed up to a defined limit)[48,49] and individualized prescriptions based on inpatient opioid use.[50]

Given the risks and adverse side-effect profile of opioids, some have questioned whether oral opioids should be prescribed routinely for all women after cesarean delivery. Informal survey data suggest that, in most countries aside from the United States and Canada, opioids are rarely or never prescribed to women who have had a cesarean delivery.[51] Future research should determine whether adequate analgesia can be obtained with the use of a combination of nonopioid analgesics, such as NSAIDs and acetaminophen.

Our recommendations for immediate postdelivery pain management after cesarean delivery among opioid-naïve women include the following (in the absence of contraindications to these medications):

- Neuraxial morphine (or hydromorphone)
- Acetaminophen: 975 mg by mouth every 8 hours standing
- Ketorolac: 30 mg intravenously every 6 hours standing for 24 hours, followed by ibuprofen 600 mg by mouth every 6 hours
- Short course of oxycodone (maximum daily dose, 30 mg or 6 5-mg tablets) as needed if pain is poorly controlled (eg, pain is interfering with the woman's ability to mobilize, breastfeed, or otherwise care for her baby, or the woman reports being unable to cope with the pain) with scheduled NSAIDs and acetaminophen alone
- If women are not taking opioids in the hospital, do not prescribe at the time of discharge.
- If women are taking opioids in the hospital, engage in a shared decision-making process to select the number of opioid tablets to be prescribed (but no more than the equivalent of 20 5-mg tablets of oxycodone). Information should be provided regarding the expected duration of pain, risks, and benefits of opioids and alternatives to opioids. Rather than prescribing the same quantity of opioids for all women after cesarean delivery, women should be allowed to choose to be prescribed a smaller amount.[48]

Pain management among opioid-dependent women

Women with opioid dependence in pregnancy are a heterogeneous group. Women with this diagnosis may have chronic pain that is treated with opioids throughout pregnancy, an OUD treated with MAT (buprenorphine or methadone), or an untreated OUD that results in the use of unprescribed or illicit opioids. There is considerable overlap among these women's physiologic characteristics because of their opioid exposure, although other associated risk

factors and comorbidities may differ in pregnancy and thus lead to differing pregnancy outcomes.

One main concern when caring for these women in labor is the undertreatment of pain in the acute setting.[52] In addition, for women with a history of OUD, there may be fear among both providers and patients of triggering a relapse to opioid misuse with the treatment of acute pain and the stress of childbearing and possible surgery.

Challenges in treating acute pain among opioid-dependent patients include the potentially high tolerance to opioids in such patients combined with opioid-induced hyperalgesia, which may result in opioid-dependent women experiencing more severe pain in the immediate postpartum period compared with women without opioid dependence.[52] Chronic opioid use and OUD also are associated with a history of childhood trauma and interpersonal violence.[53,54] Childbirth is a stressful time for many women, especially for women with a history of trauma. Such a history can diminish coping mechanisms and lead to feelings of helplessness or loss of control, which may trigger retraumatization.[55] Women with OUD may face additional concerns about the potential involvement of child welfare agencies and custody issues, guilt from having a newborn infant with neonatal withdrawal, and fears about their own risk of relapse.

Prenatal care can provide an opportunity to explore these fears, to provide education and anticipatory guidance, and to explore expectations about pain control. Many opioid-dependent women may benefit from a prenatal outpatient anesthesia consultation and consultation with a psychologist for cognitive behavioral therapy or other counseling before delivery.

Our recommendations for the management of OUD during pregnancy for women with OUD that is stabilized and maintained on MAT and women with chronic pain on opioids include the following:

- Encourage women to remain on their prescribed medications throughout pregnancy.[56] Specific to pregnancy, the goals of MAT are to suppress symptoms of cravings and withdrawal and prevent illicit opioid use that can lead to a range of adverse pregnancy outcomes. MAT also increases adherence to prenatal care and reduces infection that is associated with intravenous drug use.
- Counsel women that, because of the risk of acute maternal withdrawal and relapse, which are 2 conditions that can be harmful or fatal to both mother and fetus/neonate, acute detoxification or attempting to wean or stop opioids before delivery is not recommended for most women. Although MAT for women with OUD is considered the standard of care, some women may be motivated or prefer to undergo medication-assisted withdrawal during pregnancy. This option should be undertaken only with careful patient selection, close supervision, and appropriate behavioral and social support resources that extend into the postpartum period.
- For women who are taking chronic opioids for pain, some consideration can be made for a slow titration toward a lower dosage of systemic opioids over the course of the pregnancy.[57] The details of managing such a course fall beyond the scope of this section but, ideally, should be managed with a pain specialist.
- In preparation for labor and delivery, an interdisciplinary approach that involves the obstetric team and the addiction medicine team or methadone clinic providers should ensure that the woman signs the appropriate consent to obtain the medication dosage.

Vaginal delivery in patients with OUD

Our recommendations during labor and delivery for opioid-dependent women because of chronic pain or OUD include the following:

- Women should remain on their daily dose of MAT medication throughout labor to treat the underlying pain condition or substance use disorder and to prevent acute withdrawal.[58,59] There is evidence that dividing the dose of maintenance medication (buprenorphine or methadone) into 2–3 doses can improve pain control.[60]
- Women should be encouraged to receive neuraxial labor analgesia (epidural or combined spinal-epidural) in early labor or as soon as contractions are perceived to be uncomfortable, because this modality has been found to be highly effective in opioid-dependent women. With effective neuraxial analgesia, supplementation with systemic opioids should not be required. There is no evidence that opioid-dependent pregnant women tolerate labor worse than nonopioid-dependent women if baseline MAT is continued.[61]
- Inhaled nitrous oxide should be avoided because it may be less effective in opioid-dependent women and may increase the risk of sedation with concurrent use.[62]
- Opioid agonist/antagonists, such as nalbuphine or butorphanol, can precipitate opioid withdrawal and should be avoided.
- Postpartum pain after vaginal delivery should be managed with a multimodal approach. Additional systemic opioids may be necessary after delivery, but these medications should not be ordered routinely. Although buprenorphine is a partial agonist of the mu receptor, adequate pain relief can be obtained by providing a full opioid agonist with strong affinity for the mu receptor (eg, fentanyl or hydromorphone), if needed. Use of buprenorphine should not preclude the use of systemic opioids when needed for acute pain management.

Finally, it should be noted that women with untreated OUD may be among the most challenging to care for during labor and delivery. Management includes a careful history of all substance use, a urine toxicology test to check for other substances, monitoring for withdrawal with the use of the Clinical Opiate Withdrawal Scale or similar scale, and

pharmacotherapy for withdrawal with the use of either methadone or buprenorphine therapy. Ideally, methadone or buprenorphine therapy should be initiated in consultation and collaboration with an addiction medicine specialist or, recognizing that these specialists are not available in many settings or in every circumstance, an obstetric care provider with experience in caring for such patients.[62] Pain management is the same as that for a woman previously stabilized on MAT. However, additional challenges may be present if the parturient is using other drugs that may influence analgesia and mental status, such as stimulants or benzodiazepines.

Unscheduled or emergency cesarean delivery in patients with OUD

If a woman with OUD requires an unplanned cesarean delivery and has a functioning epidural catheter in place for labor, this can be used for the surgery. If a functioning epidural catheter is not in place, spinal or general anesthesia is usually given; the choice depends on the acuity of the situation. Postoperative neuraxial opioids have been shown to improve pain control in the nonopioid-dependent population, and their use is appropriate in opioid-dependent patients, although they may not be as effective because of issues of tolerance. A recent study of 14 women demonstrated that the use of clonidine instead of fentanyl in the epidural provided adequate pain relief in laboring and cesarean delivery patients who were also receiving buprenorphine.[63] This substitution of clonidine is a promising approach and should be studied further in this population. It should be noted that this epidural preparation may not always be readily available. Also, because epidural clonidine can cause hypotension, it should be used judiciously and with appropriate monitoring.

As in all women, among those with OUD, adjunctive methods should be used during cesarean delivery to aid with postpartum pain control. Acetaminophen, either intravenously or by mouth, should be administered as a first-line treatment of pain. Given the similar efficacy and lower cost of oral acetaminophen, it is the preferred route and generally can be used even if by mouth intake is otherwise being limited by surgery. In addition, ketorolac should be given at the end of surgery, barring any contraindications.

Additionally, given that 1 mechanism of opioid-induced hyperalgesia is phosphorylation and thus stimulation of the N-methyl-D-aspartate receptor by opioids, low-dose ketamine, which blocks the N-methyl-D-aspartate receptor, can be considered to potentiate the effects of the opioids without causing the hallucinations or nightmares that are associated with higher doses.[64,65] A single 10-mg dose of ketamine, given intraoperatively, has been shown to decrease pain scores 2 weeks after delivery.[66] Although the data regarding preoperative gabapentin (600 mg) is mixed and there is some concern about transfer into breast milk and postpartum side effects such as dizziness, the risk/benefit ratio in this population may favor its use.[67] Transverse abdominus plane (TAP) blocks may also be used preoperatively or postoperatively. Although they have not been studied in opioid-dependent patients, they may have clinical utility in this population.

Postoperatively, MAT should be continued, and the patient with OUD should be maintained on her baseline dosage of opioids. Withholding these medications does not improve postpartum pain control and increases the risk of withdrawal. As noted previously, some women benefit from receiving their usual daily dosage of methadone or buprenorphine in divided doses, because the half-life for analgesia is much shorter than for opioid withdrawal. Nonopioid scheduled multimodal analgesics should be ordered as previously described, with as-needed oral opioids available to the woman. Some patients, especially those on buprenorphine maintenance, may require more opioid pain medication than the opioid-naïve patient and may require patient-controlled analgesia with a full agonist with strong affinity for the mu receptor, such as fentanyl or hydromorphone, for 24 hours.

Women with OUD should be encouraged to breastfeed and room in with the baby, because both have been shown to improve outcomes for mother and baby and anecdotally have been shown to decrease pain medication use for the mother. In addition, selective norepinephrine/serotonin reuptake inhibitors, such as duloxetine, have been shown to improve postoperative pain control in the nonobstetric population and may be considered.[68]

Important research gaps in this area include definition of the roles of both nonopioid medications (clonidine, gabapentinoids, selective norepinephrine/serotonin reuptake inhibitors) and regional anesthesia with TAP blocks or TAP catheters and definition of optimal dosing of neuraxial opioids in opioid-dependent patients.

Scheduled cesarean delivery

In addition to the measures and steps noted earlier, the patient planning a cesarean delivery will benefit from a preoperative consultation with an anesthesiologist and a therapist who is trained in cognitive behavioral therapy. Expectations can be discussed with both the team and the woman before the woman's arrival in the labor and delivery unit. The woman should be instructed and encouraged to stay on her stable dosage of opioids and take her morning dose before arriving for surgery.

Nicotine replacement

Because a large percentage of women with OUD are also nicotine dependent, smoking cessation must be addressed in the prenatal period. Nicotine is a central nervous system stimulant and has analgesic properties. As such, nicotine withdrawal during the postpartum period can diminish pain tolerance and increase opioid requirements.[68] Nicotine replacement therapy therefore should be provided.

Discharge pain medications

Women who are taking opioids for chronic pain likely will need additional opioid medication on discharge. Issuing a prescription that dispenses small amounts encourages these patients to receive follow-up examinations and can help ensure that the medication is not being used inappropriately. This follow-up can be coordinated with the patient's pain medication provider. For women with OUD who are receiving MAT, decisions about discharge medications should be based on a conversation with the woman about her fears of opioids in the home and should be determined, ideally, with the individual or team managing her MAT. Some patients in recovery are understandably wary about having a prescription for opioids, but this reluctance should not prevent their use if pain medication is needed. Women should be made aware that untreated pain can also be a trigger for relapse.[69] Providers should explain that safeguards can be used if needed, such as having a reliable family member dispense the medication. Researching a woman's pain medication requirements during hospitalization can provide a starting point for the amount of medication to prescribe on discharge; a shared decision-making approach is encouraged. As with opioid-naïve patients, the treatment of acute pain rarely requires more than >3 days of pain medication. For the woman on methadone, the discharging provider should communicate with the outpatient opioid treatment program regarding her in-hospital dosing postpartum and additional pain medications given. The woman with untreated substance use disorder before delivery should maintain priority for admission to a treatment program, or, if feasible, an in-person handoff to an addiction provider should be made while she is in the hospital.

Management modalities for pregnant women with OUD

Pregnancy as a window of opportunity for treatment

Pregnancy is a window of opportunity for the treatment of chronic diseases, which includes substance use disorders. During this time, women have access to health insurance and often are motivated toward positive health behaviors in an effort to invest in the health and well-being of their future children.[70] Similar to the treatment of other perinatal chronic diseases (eg, diabetes mellitus, hypertension, connective tissue disease), obstetricians have an opportunity to provide care for substance use disorders during pregnancy that will reduce maternal, obstetric, fetal, and newborn infant morbidity and mortality rates and potentially decrease generational transmission of this chronic condition.[71–74] High-quality, evidence-based treatment interventions during this time have the potential to improve maternal and child health and have far-reaching health benefits for future generations.[75]

Standard of care in the treatment of OUD in pregnancy

The standard of care for the treatment of perinatal OUD includes MAT with either methadone or buprenorphine.[56] A recent Cochrane review of studies that compare the efficacy of methadone vs buprenorphine for the treatment of perinatal OUD did not identify 1 pharmacotherapeutic agent as superior to the other.[76] Individual studies offer evidence of small differences in outcomes, which suggests, for example, that those who were treated with methadone are more likely to be retained in treatment and that treatment with buprenorphine may reduce the severity and frequency of NOWS.[76–78] Both medications are acceptable treatment options, and the choice between them will be guided not only by data regarding outcomes but also by differences in the systems providing treatment. Shared decision-making is particularly useful when there is >1 acceptable treatment option; this approach is recommended when pregnant women are considering pharmacotherapy for the treatment of OUD.[56] Among other possible elements, such conversations should consider the benefits and burdens of daily visits for dosing as opposed to the option for prescription that allows women to take their medication at home with less frequent clinic visits (for methadone vs buprenorphine, respectively) and be informed by an individual's past experience with either, if any, treatment.[79]

Methadone

Methadone, a full mu-opioid receptor agonist, is effective for the treatment of perinatal OUD.[56] Methadone must be administered at a federally accredited opioid treatment program, and patients must receive their dose daily under direct observation. Access to opioid treatment programs that provide methadone may be limited in certain geographic locations. Even if distance is not prohibitive, the need for regular and reliable transportation may limit access to this treatment option for patients with OUD.

Use of methadone in combination with a comprehensive care program for the treatment of perinatal OUD has been associated with reduced pregnancy complications, higher birth weights, decreased HIV risk behaviors, decreased fetal mortality rate, and improved adherence to prenatal care compared with no treatment.[80] Pregnant women who receive OUD treatment that includes methadone were more likely to have fewer relapses to drug use and were retained in treatment longer compared with pregnant women who received OUD treatment with buprenorphine.[81] Ideal candidates for treatment with methadone include those with (1) a history of successful use of methadone, as judged by abstinence from other opioids or other outcomes such as improvement in daily functioning (eg, ability to retain employment, to parent, and to engage in prenatal or medical care); (2) a history of intravenous drug use or severe OUD that would benefit from the structure of a methadone clinic with directly observed therapy, or (3) an inadequate

response to buprenorphine. It is critically important that the feasibility of continuing methadone during the postpartum year is discussed, and plans are made to support this treatment choice.

Methadone is known to prolong the corrected QT (QTc) interval. Caution should be taken if QTc is >450–499 msec. An alternative therapy should be strongly considered if QTc is ≥500 msec.[81]

The aims of pharmacotherapy with methadone are to alleviate withdrawal symptoms and reduce cravings.[82,83] The initial dosage of methadone is usually 20–30 mg and is generally titrated gradually over weeks to a dosage of 80–120 mg per day. However, some pregnant women will require significantly higher dosages. Alternatively, the methadone dosage may be titrated over days in the inpatient setting. Because dosages are titrated, it is important to understand that the half-life of methadone is 24–36 hours. Treatment with methadone, in contrast to buprenorphine, does not require that women experience withdrawal symptoms at the time of the initiation of pharmacotherapy.

Women on a stable dosage when not pregnant may require dosage adjustments during pregnancy because of an expanded volume of distribution and progesterone-increased cytochrome P450 metabolism of methadone.[84] These normal physiologic changes during pregnancy can result in decreased levels of methadone, particularly during the second and third trimesters. However, adjustments are needed only if the current dosage is not sufficient to prevent withdrawal symptoms or reduce cravings. Split doses or a dosage increase may be necessary to prevent cravings and withdrawal symptoms during pregnancy. To avoid the risk of methadone overdose during induction, splitting doses and dosage increases should not be undertaken at the same time.

Buprenorphine

Treatment with buprenorphine, a partial mu-opioid receptor agonist, is available in office-based settings in addition to being available through opioid treatment programs. Health-care insurances generally will cover the cost of buprenorphine, and the office-based treatment setting makes buprenorphine an accessible and appealing treatment option for many patients. Health-care providers who wish to prescribe buprenorphine must first complete a training program to obtain a waiver from the Drug Enforcement Administration. Although the number of waivered health-care providers, including many obstetric care providers, has increased since 2012, many areas of the country are without waivered providers, particularly in rural areas. One recent study has found that more than one-half of rural counties (60%) lack a health-care provider who has received a waiver to prescribe buprenorphine.[85] In addition to the use of prescribed doses of medication, experts recommend that patients who receive buprenorphine attend at least monthly counseling sessions. However, fulfilling this recommendation can be challenging, given the significant gaps between OUD treatment needs and available capacity in the United States.[86]

Studies have demonstrated both the safety and tolerability of buprenorphine in pregnancy. The Maternal Opioid Treatment Experimental Research trial, a double-blind, double-dummy, randomized controlled trial of 175 pregnant women with OUD, compared maternal, obstetric, and newborn outcomes in women who received buprenorphine vs those who received methadone.[77] Although there was no significant difference between the groups in the incidence of NOWS (the primary outcome for the study), newborn infants who were exposed to buprenorphine during pregnancy required less medication to treat NOWS and had a shorter duration of treatment and hospital stays compared with newborn infants who were exposed to methadone during pregnancy. Secondary outcomes such as birthweight, birth length, and gestational age were also more favorable in newborn infants who were exposed to buprenorphine compared with those who were exposed to methadone. There were no differences in maternal outcomes that included the rate of relapse as measured by urine screening tests, rates of cesarean delivery, maternal weight gain, number of prenatal care visits, or analgesia used at delivery. Although women who received methadone had more nonserious maternal events overall and nonserious maternal cardiovascular events in particular, the 2 groups did not differ in their rate of serious maternal or neonatal adverse events. Women who received methadone were more likely to complete the study compared with women who received buprenorphine.

Ideal candidates for treatment with buprenorphine include those with (1) a history of a good past response to buprenorphine, (2) availability of a buprenorphine prescriber and the woman's ability to engage with this health-care provider, and (3) an inadequate response to methadone. As with methadone, the feasibility of continuing buprenorphine during the postpartum year should be established during pregnancy, and plans should be made to support this treatment choice. In women for whom both methadone and buprenorphine are appropriate and accessible, methadone may be more appropriate if there is concurrent use of benzodiazepines or other central nervous system depressants. However, in situations in which buprenorphine is the only accessible or otherwise preferred pharmacotherapy, it should not be withheld from women concurrently using benzodiazepines. The FDA instead recommends careful medication management.[87]

Buprenorphine monotherapy (eg, Subutex), in contrast to combination therapy with buprenorphine and naloxone (eg, Suboxone), historically has been recommended for pregnant women because of theoretic risks to the fetus if withdrawal is precipitated by the naloxone component. However, although data about the safety of buprenorphine plus naloxone or buprenorphine alone during pregnancy are limited, they do not support this theoretic concern.[56,88] For women who become pregnant while on combination

therapy, continuation of buprenorphine with naloxone is recommended by some experts.

The initiation of buprenorphine, referred to as buprenorphine treatment induction, requires that women must be experiencing opioid withdrawal symptoms; otherwise, initiation of buprenorphine can precipitate acute opioid withdrawal. It is recommended that women abstain from short-acting opioids at least 12–24 hours before induction and long-acting opioids 36–48 hours before induction. The presence of at least mild withdrawal symptoms should be verified by the administration of a validated opioid withdrawal scale.[56] Women who experience at least mild withdrawal symptoms can receive a 2- to 4-mg dose of buprenorphine, and a validated opioid withdrawal scale should be repeated in 30 minutes.[56] If the woman tolerates this initial dose, another 2- to 4-mg dose of buprenorphine can be administered. A recent meta-analysis has found that a daily dosage of 16 mg is sufficient to suppress illicit opioid use in most pregnant women with OUD.[89] However, sufficient dosages vary and can range from 4–24 mg daily. Compared with methadone, there are fewer data available about the pharmacokinetics and pharmacodynamics of buprenorphine during pregnancy. Limited data suggest that higher -and, more frequent doses (2–4 times daily) may be required during pregnancy, with dosage requirements increasing with increasing gestational age.[90–92]

In patients who are unable to tolerate buprenorphine or in whom buprenorphine is found to be ineffective, methadone is recommended.[56] In the absence of sedation, switching from buprenorphine to methadone can be done immediately; in contrast, switching from methadone to buprenorphine can be challenging, given the long half-life of methadone and the risk for precipitating withdrawal symptoms with the administration of buprenorphine. Although transitioning from methadone to buprenorphine is possible with close monitoring, only 1 study with a small sample of women (n=20) in whom the transition was made out of necessity has been performed.[93]

Fetal and neonatal effects of MAT

The most consistent and common adverse effect of the use of methadone or buprenorphine during pregnancy is NOWS. Other fetal side effects include reduced fetal activity and heart rate and fetal growth restriction.[84] The use of methadone or buprenorphine during pregnancy has not been associated with an increase in birth defects.[56] Longitudinal studies that have examined developmental outcomes have demonstrated minimal to no long-term neurodevelopmental impact, particularly when comparing opioid agonist–exposed vs nonexposed children from similar socioeconomic groups.[56,84]

Naltrexone

Although the FDA has approved naltrexone, an opioid antagonist, for treatment of OUD, data are insufficient to support the initiation of naltrexone therapy during pregnancy. Animal studies in rats and rabbits have associated naltrexone with early pregnancy loss, albeit at dosages significantly exceeding those that are therapeutic in humans, but these studies did not find an increased risk of associated congenital malformations.[94] In humans, although no specific adverse pregnancy outcomes have been linked to the use of naltrexone, clinical data from an examination of the risks associated with naltrexone use during pregnancy are limited by small sample size, lack of control groups, or minimal control for confounding variables.[95–99] With these important limitations noted, retrospective analyses of experience in small groups of women from Western Australia who were treated with naltrexone implants during pregnancy concluded that "the use of implant naltrexone during pregnancy was not associated with higher rates of negative birth outcomes compared with methadone- and buprenorphine-exposed neonates" and suggested lower rates of NOWS and shorter neonatal hospital stays among the group treated with naltrexone than in the group treated with methadone.[95] Continuation of naltrexone in women who use this agent and become pregnant requires a careful assessment and communication of the risks of discontinuing naltrexone (eg, risk of relapse) and the limitations of data surrounding use in pregnancy so that women can make an informed treatment choice. Because extended-release naltrexone is a long-acting opioid antagonist, continuation of this drug may complicate pain management that is associated with medical or obstetric procedures, labor, delivery, and postpartum recovery. An anesthesia consultation before delivery is recommended, and adequate pain management strategies and guidelines need to be in place for women continuing naltrexone during pregnancy.[100]

Medication-assisted withdrawal

Currently, available evidence and its limitations do not support routinely offering opioid detoxification, also termed medication-assisted withdrawal, during pregnancy to most patients. In the largest systematic review to date that included 1126 pregnant women with OUD who underwent opioid detoxification, rates of successful detoxification (9–100%) and illicit drug use (0–100%) were widely variable.[101] The high rates of successful detoxification (as high as 100% in some studies) as judged by no evidence of opioid use recurrence on urine drug screen at the time of delivery occurred in studies in which women were in inpatient residential treatment programs, including involuntary institutionalization. The rates of relapse were dependent on the inclusion or exclusion of women who were lost to follow-up. In a separate review, rates of relapse appear to be lower in women who complete longer tapers and more intensive care over a longer period of time, but estimates still vary widely.[102–104] Previous work to date strongly suggests

that rates of relapse after detoxification in pregnant women with OUD, although not well-known, are likely high. Similarly, given the significant bias and poor-to-fair quality of previous studies, at present any risks for pregnancy, fetal, and newborn complications that are associated with opioid withdrawal during pregnancy remain both unidentified and unquantified.[101] The elements of optimal care for pregnant women who choose medication-assisted withdrawal have not been well described, and future research in this area is needed before it can be recommended as a standard option.

Despite the available evidence against medication-assisted withdrawal for pregnant women with OUD, some women may prefer this option, given the known risks, which includes the risk of NOWS, that are associated with continuing pharmacotherapy for the treatment of OUD during pregnancy. A shared decision-making tool is available to assist patients and health-care providers in discussing the decision to continue or taper buprenorphine or methadone during pregnancy and ensure that women are making informed, evidence-based decisions that reflect their values and preferences.[105]

Other components of pregnancy care for women with OUD

Antenatal counseling and care

Pregnancy care for women with OUD includes care for those receiving pharmacotherapy, those who undergo medication-assisted withdrawal, and those who decline treatment. In addition to standard prenatal counseling, specialized anticipatory guidance for this population should include antenatal education about NOWS, the OUD-related benefits of breastfeeding, prevention of sudden infant death syndrome, expectations for the involvement of social services, and counseling about postpartum pain control options and contraception.

NOWS occurs in approximately 40–60% of neonates who are born to women who receive opioid agonist pharmacotherapy.[77] There is no correlation between NOWS and opioid agonist dosage.[106] If NOWS occurs, it usually becomes apparent within 2–5 days after birth.[107] Obstetricians, midwives, or other prenatal care providers usually provide anticipatory education for women and families regarding NOWS, but consultation with pediatric or neonatal care providers before delivery may also be helpful. Parents should be informed about expected neonatal symptoms, treatment, and length of stay in the hospital.

Breastfeeding has been shown to decrease NOWS severity, reduce the need for treatment of NOWS, and decrease neonatal length of stay in infants born to women with OUD receiving pharmacotherapy.[108–110] Women should be aware that breastfeeding is not advised if there is concurrent use of illicit substances, which includes cannabis, because of the potential for adverse neonatal outcomes.[111] In the United States, breastfeeding is contraindicated for women with HIV infection. In contrast, breastfeeding is not contraindicated for women with hepatitis C virus (HCV) infection.[112] Women with HCV may have significant hesitation and fear about breastfeeding based on inaccurate information obtained from peers or other health-care providers; reassurance and counseling regarding best evidence should be provided in such cases.

As noted earlier, women with OUD may also have significant concern about pain control after delivery. An antenatal anesthesia consultation may alleviate some of these concerns and initiate a process of shared decision-making about postpartum prescription opioid use.

In the setting of ongoing or anticipated illicit opioid use, counseling about harm reduction in pregnancy is important and includes the provision of prescriptions or information about how to access naloxone and education about how to administer it. Options for obtaining naloxone include prescribing by the provider, receiving it from a pharmacy without a prescription under a standing order, or through attending overdose training that is provided by local public health entities. For patients who continue the use of illicit opioids, syringe exchange programs and supervised injection sites are proven public health interventions that reduce the harms that are associated with opioid and other substance use, although such options and programs are not available in many places. Patients should be provided with information about accessing these services in locations where they are available.[113,114] Education should also be provided about avoidance of central nervous system depressants, particularly benzodiazepines.[115,116]

Women with OUD should be offered information and guidance regarding anticipated social service involvement with the woman and family after delivery. Obstetric care providers should familiarize themselves with the laws in their state with regard to the reporting of substance use and prepare patients for the involvement of social services.

Separate from the counseling just described, care for women with OUD in pregnancy should include screening or testing for conditions with increased prevalence in such populations. Co-occurring substance use disorders; psychiatric illness; intimate partner violence; poor social support; and psychologic, physical, and sexual trauma are common among women with OUD. Certain infectious diseases, including HIV, HCV, hepatitis B virus, tuberculosis, and sexually transmitted infections, are more common in women with OUD because of sharing of paraphernalia, sex work, and incarceration. We recommend testing to identify these infections.

Antenatal fetal assessment

With regard to fetal growth assessment and antenatal testing, there is significant heterogeneity of practice, and individualized plans are recommended. Most obstetric providers recommend at least 1 fetal growth scan in the third trimester because of an association of OUD with low birthweight and small for gestational age Infants.[117–119] Some obstetric providers recommend serial growth scans in the

case of ongoing use of illicit substances or tobacco. Similarly, although data to support antenatal testing with nonstress testing or biophysical profiles are limited,[120] some obstetric providers recommend such testing in the setting of ongoing use of opioids, including pharmacotherapy.

In the absence of coexisting obstetric indications, delivery at <39 weeks of gestation is typically not recommended. Details of the management of pain during labor and delivery are outlined in the section, "Pain management during pregnancy and the postpartum period."

Postpartum management

Postpartum support should be provided for women so that they continue or initiate MAT to treat OUD after delivery. Women are at particularly high risk of overdose and death in the first year after delivery.[121] There are significant stressors in the postpartum period for this patient population, including changes in access to care, threats of loss of child custody, and care of infants who experience NOWS. Accordingly, very close follow-up is recommended after delivery.[122] Obstetric providers must be advocates who argue against the separation of women and their infants on the basis of substance use disorder alone.

Research has demonstrated significant disparity in the substance use disorder population with regard to contraception.[123–125] Long-acting reversible contraception should be offered, immediately after delivery if available, but such offers and all contraception counseling should be provided within a framework of reproductive justice with the goal of empowering women to achieve their desired interpregnancy spacing and family size and to make corresponding contraceptive choices. Judgments about a woman's suitability for parenthood should not drive contraceptive counseling in general or recommendations regarding specific methods among all of the available and appropriate options.

Although pregnancy serves as a window of opportunity for the initiation of treatment for OUD and the establishment of positive health behaviors, it is important that this opportunity not be lost after delivery. Transition of care to a primary care provider is crucial in the postpartum period and is best accomplished through warm hand-offs. Follow-up medical care, which includes treatment of tuberculosis or HCV, should be arranged before a woman is discharged from obstetric practice and care.

Future research and clinical issues

Although evidence exists in some areas to guide the pregnancy care of women with OUD, clinical and research questions remain. There is, for example, a lack of data about the benefits, risks, and safety of naltrexone use during pregnancy. Given its use and utility in other patients, a study of naltrexone and inhiation of such treatment in pregnancy is needed.[100] Additionally, newer subcutaneous formulations of buprenorphine have not been studied in pregnant women. Given the physiologic changes during pregnancy and the possibility of dosage adjustments for both methadone and buprenorphine, future research should investigate the pharmacodynamics and patient acceptability of different medication formulations. Importantly, although there is significant interest in medication-assisted withdrawal, well-designed research is needed both to understand the risks and benefits of this option and to identify the women best suited for such treatment. Obstetric care providers must advocate for the inclusion of pregnant women in research regarding OUD because clinical trials (including FDA studies) commonly do not include pregnant women.

The transition of care during the postpartum period also requires study. Researchers should investigate the role of ancillary services (such as home visiting and peer counselors) in providing support in the vulnerable postpartum period. Finally, obstetric care providers are not well-trained in the provision of behavioral health in general or substance use disorder treatment in particular. The attention brought to the opioid crisis should be used to study how to better integrate behavioral health into all spheres of women's health and how to train obstetric care providers to assess, treat, and refer for substance use disorders.

Care models and integration of services to support OUD management during pregnancy

Although the ongoing opioid epidemic continues to have a significant impact on the health and well-being of substantial numbers of pregnant women and their newborn infants in the United States, significant barriers still exist that prevent women and their infants from accessing the optimal care that would allow successful pregnancy outcomes. OUD increases the risk of maternal, obstetric, fetal, and neonatal morbidity and death, but MAT during pregnancy has been shown to improve adherence to prenatal care and reduce the risks of pregnancy complications.[126] However, many states, often driven by concern for fetal or neonatal "victims," consider substance use by pregnant women to be a criminal offense. Accordingly, many women fear that seeking help for substance abuse during pregnancy could result in their arrest and prosecution with subsequent placement of their children in foster care.[127] Even in states without such laws, the social stigma faced by pregnant women with substance use disorder drives many away from the care that they and their infants need.

In the absence of consistent application of policies and protocols for pregnant women with OUD, many pregnancy care providers have devised individual programs within their practices and health-care systems to care for the growing number of women who require OUD treatment before, during, and after pregnancy. It is now widely accepted that treatment of OUD is most successful when it is viewed as a chronic illness rather than a moral failing or weakness. Women with OUD require an "all hands on deck" approach to care, in which a broad range of medical, social, and behavioral services are needed to address not only the

medical issue of substance abuse but also the social and economic disparities that often accompany it. In addition, current research suggests that adverse childhood experiences increase the risk of substance abuse later in life, and that providing these women with appropriate behavioral therapy is a necessary adjunct to treatment and healing future generations within a family.[128]

This section describes 2 types of care models that have been proposed for the treatment of pregnant women with OUD during pregnancy: (1) a collaborative care model, in which various agencies and health-care providers form a partnership to facilitate patient access to these resources and (2) a "1-stop shop" model, in which colocated resources are provided to patients at a dedicated office or other facility, often as part of a large health-care institution, such as a hospital or health-care center. Although both models of care provide treatment of these women and their families during pregnancy and in the postpartum period, they differ in how these services are delivered to patients. Each model has both advantages and disadvantages. It is important to note that no 1 model should be thought of as the sole solution for management of OUD during pregnancy. Instead, models of care should be adapted to fit individual communities, available resources, and the specific issues and problems faced by the population that is to be served.

Collaborative care model

Although addiction medicine services, social services, and support groups are often available within health-care systems and the community at large, a lack of communication and coordination between providers of these services and obstetric care providers can make it difficult for pregnant women with OUD to access them fully. The collaborative care model seeks to remedy this problem by gathering all of the available medical and social support resources within a community and bringing these resources to patients, often by crossing the usual boundaries of community and clinical care.[56] Participating partners in a collaborative care model ideally should include residential and outpatient recovery centers that offer MAT services, obstetric and maternal-fetal medicine services that provide prenatal care, and level III neonatal intensive care units and pediatric care for treatment of NOWS. In addition, other groups and agencies, such as Healthy Start, Planned Parenthood, and state or local departments of public health, may provide services such as contraception counseling, breastfeeding education, and ongoing health care.

An essential aspect of some collaborative care OUD programs is the endorsement by and cooperation with the local court system. For example, local law and justice systems may agree to waive fees and jail time for patients who enroll in the program and demonstrate a strong commitment to it by keeping prenatal care appointments, screening negative on drug screening tests, attending support groups, and completing hospital tours. Children's health services and parenting education are also important components of these partnerships. Coordination with mother and infant educational and intervention programs that may already exist within residential facilities or other agencies can be established to offer group and individual counseling and parenting, nutrition, and life-management classes. An example of such a comprehensive collaborative care OUD program is the Addiction Support and Pregnancy coalition that was developed in Sarasota, FL.[129]

Pregnant women with OUD often have chronic health problems in addition to substance abuse. Common concurrent health problems include HCV infection,[130] sexually transmitted infections, poor dental care or dentition, inadequate nutrition, and tobacco use.[131] Pregnant women with OUD are more likely to have coexisting psychiatric disorders that include major depressive disorder, posttraumatic stress disorder, and panic disorder.[132] Many women also live in substandard housing, are unemployed, and have a history of sexual abuse, intimate partner violence, or sexual assault.[133,134] Collaborative care offers the opportunity to address these and other co-occurring health issues during pregnancy. Interaction with different agencies and health-care providers who participate in a collaborative care coalition exposes these women to the possibility of continued care for themselves and their families throughout their lives. For example, with the expansion of Medicaid services in most states as a result of the Affordable Care Act, pregnant women on Medicaid often remain eligible for these health services after their babies are born. Collaborative care program partnerships provide information and help with accessing Medicaid health services and ensuring that they continue for women who qualify.

A disadvantage of the collaborative care model is that, although it has designated partners among various agencies, patients are still required to travel to the various participating agencies and facilities to access services.

BOX 1
Types of services needed to support opioid use disorder management during pregnancy

Hospital services, including specific women and children services tours
Obstetric care provider
Pharmacotherapy provider
Behavioral health services
Community services, including child care
Social services
Department of Children and Families
Law enforcement and court system
Pediatric care providers
Support groups
Breastfeeding support
Contraception counseling

Finding reliable transportation can be problematic for many patients, who often rely on public transportation and who have competing priorities of child care and employment. Child care and housing are also major concerns for patients. Collaborative programs must consider the transportation and child-care needs of their clients to ensure that they can keep appointments and fulfill the requirements of the program to avoid legal penalties.

Another disadvantage of collaborative care programs is that some communities do not have a full array of resources that pregnant women with OUD require for successful treatment (Box 1). At a minimum, it is thought that a collaborative care model should include a dedicated MAT provider and a staff member who is charged with triage and coordination of existing services for patients. Not all collaborative care practices have the staff or means to establish a formal coalition of services and resources; however, much can be done on a small scale to facilitate access to resources and to direct patients to the services that are most needed.

Colocation of services: "1-stop shop" models

The basic principle underlying the "1-stop shop" model of care is to provide women with all of the services they need to manage their substance use disorder during pregnancy at a single facility or office that is dedicated to this purpose. At 1 location and often during a single visit, pregnant women with OUD can access a wide range of services that include MAT, prenatal care, social services, and legal aid within a supportive, nurturing environment. This model limits the necessity of scheduling and finding transportation for multiple appointments that may be located far away from each other; many such care models also provide on-site child care for women with appointments or who are accessing services.

Another advantage of the 1-stop shop program is that it can encourage and support a group model of care, in which a variety of resources are brought and presented together to many patients who share similar needs.[135] Group care models have also been shown to increase patient education and satisfaction while improving practice efficiency and reducing repetition.

A disadvantage of this type of care model is that the cost of a dedicated facility and staff is often prohibitive. The volume of patients or the space available may not allow all providers to be busy at once, a limitation that, from a provider's perspective, can reduce the efficiency of this type of model. In addition, such programs require an intense and complex level of organization and diverse staff to carry out the various program components. When such realities limit the size of the staff that can be brought together, a 1-stop shop could perhaps function with a minimum of a behavioral health counselor, such as a social worker; an obstetric care provider; and an MAT provider.

An additional disadvantage of this type of care model is that enrollment in such a program could be associated with stigma. As a stand-alone, dedicated program, patients may be identified easily as participants, which could create privacy issues and may discourage women from seeking help from such programs.

Other innovative models

Both collaborative and colocated models allow for local innovation and experimentation. For example, the OUD in pregnancy program at the University of Tennessee Medical Center at Knoxville offers detoxification in addition to MAT to women who prefer and who qualify for this type of treatment. In general, detoxification during pregnancy has not been a preferred treatment option because of the increased risk of relapse that is associated with opioid withdrawal. In pregnant women, relapse can have serious consequences, which include accidental overdose because of decreased tolerance, obstetric complications, and abrupt cessation of prenatal care.[11] However, for women who want to detoxify, the University of Tennessee Medical Center at Knoxville program facilitates this option with an MAT provider and follows the woman closely throughout the process with antenatal testing until delivery to minimize relapse and protect against other adverse outcomes. Throughout the detoxification process in this program, behavioral health management is mandatory; such management continues for at least 6 months after delivery. Research suggests that ongoing psychologic support during the detoxification process is linked to improved outcomes for both the pregnant woman and neonate. Infants born to women who receive intense psychologic support while undergoing medication-assisted withdrawal have lower rates of NOWS than women who do not receive such counseling.[103] The University of Tennessee Medical Center at Knoxville program also coordinates with the local department of children's services; this involvement is discussed with the women who seek to detoxify before their enrollment. Extensive outpatient follow-up after delivery and long-term behavioral health support, which includes breastfeeding counseling, continuous psychologic and substance use disorder counseling, contraception counseling, and social services, are integral to the program and has contributed to its success.

This and other innovative models are best offered in a context that collects outcome data to allow providers and patients to evaluate benefits and risks.[136] Ideally, comparing such outcomes to appropriate controls will allow for program improvements, expansion when benefits are clear, and the limiting or closing of innovative programs when benefits are unclear or risks outweigh benefits. Finally, as with any new or experimental treatment, all patients being offered and considering care through innovative models should understand how such models differ from standard models of care and should be offered standard care as an option.[136] In this context, it is important to note that, as part of the detoxification program discussed earlier, women are offered a choice and for

those who choose not to detoxify, standard MAT is also provided, along with a full array of medical and social services that address the specific needs of this patient population.

Conclusions and future research directions

As the opioid epidemic continues in the United States, more obstetric care providers will be called on to offer comprehensive care to pregnant women with OUD. Models of care that connect patients with the diverse resources and services that are needed to support women and their families must address the unique psychosocial, medical, and psychiatric comorbidities of this population. Guidance is beginning to emerge to help obstetric and other health-care providers construct optimal care models that are also adaptable to individual communities. Examples of such guidance can be found at the following web sites:

- Clinical Guidance For Treating Pregnant and Parenting Women With Opioid Use Disorder and Their Infants (Substance Abuse and Mental Health Administration, 2018; https://store.samhsa.gov/product/Clinical-Guidance-for-Treating-Pregnant-and-Parenting-Women-With-Opioid-Use-Disorder-and-Their-Infants/SMA18-5054)
- A Collaborative Approach to the Treatment of Pregnant Women with Opioid Use Disorders (Substance Abuse and Mental Health Administration, 2016; https://store.samhsa.gov/system/files/sma16-4978.pdf)
- The National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use (American Society of Addiction Medicine; 2015; https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf)
- Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy (World Health Organization; 2014; http://www.who.int/substance_abuse/publications/pregnancy_guidelines/en/)

Future research is needed to determine the care model that results in the best outcomes for women, their infants, and their families; protects patient autonomy; shields patients from punitive consequences of seeking treatment; and is cost-effective. Studies should identify the most efficient and cost-effective infrastructure and staffing requirements necessary to provide the best pregnancy outcomes. Studies of long-term maternal and neonatal outcomes would help inform stakeholders by identifying those interventions that bring the most value and those that have little or no value or that are cost prohibitive. Training protocols for staff must be delineated. In addition, research should be directed at management strategies for comorbidities, which include HCV infection, nicotine use, and sexually transmitted infections.

Drug testing: ethics and law

The opioid epidemic in the United States is a national health crisis with unique relevance for pregnant women and their newborn infants. The ethical issues that underlie this crisis are made even more complex when considered within the unique context of pregnancy and have tended to focus on the perinatal aspects. However, there are also broader societal and legal implications that must be taken into account, particularly as they apply to screening for substance use during pregnancy.

The ethical issues of greatest importance in discussions about how the opioid epidemic affects pregnant women and their newborn infants in the United States are autonomy (a person's right to choose whether to undergo any procedure or test), truth (honesty in disclosing plans and consequences), justice (people being treated equally, regardless of race, gender, or age), nonmaleficence (assuring no harm from medical acts), and beneficence (pursuing best interests). The first 4 principles focus primarily on the woman; the last incorporates the interests of the fetus and neonate as well as those of the woman.

An overarching foundational belief, one that provides a framework for our consideration of this problem, is that substance use disorder is a disease, not a moral failing. That belief might suggest that physicians should approach this problem the way they approach equally common, but less socially fraught medical problems, with screening and treatment. But the issue of substance use disorder requires a unique contextualization to appreciate the potential unintended consequences of the use of that standard approach. As an example, on most obstetric services, all women are screened for abnormal glucose tolerance. If a woman is found to have diabetes mellitus, it is recommended that she pursue ongoing monitoring and treatment. Similar to opioid use, diabetes mellitus can have adverse effects on the fetus and newborn infant; in some cases (eg, potential teratogenicity), the risks to the fetus from diabetes mellitus may be even greater than the risks from substance use disorder. However, physicians are not compelled to report women with elevated glucose levels to civil authorities. If a woman's glucose values reflect poor compliance with diet and if their newborn infants have symptoms of hypoglycemia, society does not label them as recidivists and place the custody of their children in peril.

In contrast to the example of diabetes mellitus, women who are identified with and treated for substance use disorder can find themselves labeled as child abusers and their rights as parents challenged, even for following treatments that are prescribed by their providers. Indeed, physicians themselves may sometimes believe that they are inviting harm or a family's disruption by screening for and identifying their patients as needing treatment for substance use disorder.[137] For example, in New Jersey, a woman who had been adherent to methadone treatment was determined to

have abused and neglected her newborn infant because her infant experienced NOWS. She was convicted of child abuse, although 3 years later the state supreme court ultimately overturned the decision.[138]

Thus, those crafting a strategy to identify women who use opioids must be cognizant of the reality that the social consequences of a positive drug test for both a woman and her child can be serious and far-reaching. In the United States, 18 states define substance use as child abuse, and 3 states consider it grounds for civil commitment.[127] Some states that do not recognize this definition of substance abuse can arrest, prosecute, or incarcerate pregnant women for drug use. In light of this recognition, it is helpful to explore the options that are available to health-care providers to diagnose and treat substance use disorder during pregnancy.

It is important to start this discussion by clarifying terminology. *Screening* refers to questionnaires that allow providers to stratify patients by risk or actually identify those drug users who self-report. *Testing* refers to the analysis of biologic specimens to detect metabolites of opioids. *Universal* means that screening or testing are performed on all pregnant women. *Selective* means restricting screening or testing to those perceived to be above some threshold of risk. Selective testing could include a protocol in which specimens are assessed on the subset of women whose screening test results identify them as being at higher risk.

Focusing attention on only those with risks (a selective approach to screening) has the attraction of potentially requiring less time and resources; precedents for that approach abound. For example, cervical cancer screening is not recommended until age 21 years because infection with human papillomavirus, the agent that causes cervical cancer, is likely to resolve on its own in women younger than that age. However, there are 2 main arguments against the use of this approach to screen for OUD: unreliability and bias. In regard to the former, the inability of providers to reliably and accurately match risk factors with screening policies has been demonstrated repeatedly. The migration of screening policies for hepatitis in pregnancy away from risk-based and toward routine screening reflected the Centers for Disease Control and Prevention's awareness of the inability of providers to remember most of the specific groups at risk for that infection.

More problematic, regarding drug testing, is bias, specifically the conflation of race and other sociodemographic variables and risk. Many studies have demonstrated racial bias in prenatal drug testing.[137] In a classic article by Chasnoff et al,[139] urine samples were collected anonymously for toxicology screening over 6 months to evaluate the prevalence of substance use in 1 Florida county. That information was compared with how testing had been used clinically (during that time, 133 women were reported to health authorities after delivery for substance use during pregnancy). Despite similar rates of substance use among black and white women in the study (based on assessment of the anonymously collected urine samples), black women were reported to social services at approximately 10 times the rate for white women ($P<.0001$), and poor women were more likely than others to be reported. Similar findings have been reported more recently. For example, Ellsworth et al[140] used the electronic medical records of newborn infants and their mothers to determine which mother-infant pairs had documented evidence of meeting the criteria for illicit drug exposure screening that were set forth in the guidelines of their neonatal intensive care unit. They then assessed the rates of drug screening among 2121 mother-infant pairs to determine the strongest predictors of whether an infant was screened. Infants who were born to black women were more likely than those who were born to white women to have screening performed, regardless of whether they met screening criteria (35.1% vs 12.9%; $P<.001$) or did not (5.3% vs 1.2%; $P<.001$). In a logistic regression analysis, black race remained associated independently (odds ratio, 2.17; 95% CI, 1.25–3.79) with drug screening, even when the researchers controlled for the standard screening criteria and income, insurance status, and maternal education.

How does this imbalance happen? One mechanism whereby race becomes a surrogate for drug use risk is implicit bias. This is less obvious to both the subject and the object of the bias than is explicit bias. The latter involves explicit acts or the use of the language of racism. Implicit bias, although more common, is subtler and more insidious. Instead, implicit bias reflects the subconscious associations almost everyone makes between groups and stereotypes.

Implicit bias is not unique to pregnancy. However, a bias that is unique to pregnancy is how society views the fetus and the pregnant woman's obligations to it. In accordance with research that demonstrates that the identification of a specific victim may be associated with greater moral opprobrium, even if actual harm is limited,[141] it is possible to speculate that those who view a substance use disorder as a moral failing will view pregnant women as particularly culpable, because it would be difficult to conjure a more vulnerable victim than a fetus/neonate. In fact, surveys have shown that 52% of physicians believe that drug abuse in pregnancy should be defined as child abuse and neglect (for the purposes of removing the child from the custody of the mother) and that 23–34% physicians support incarceration for drug abuse in pregnancy.[142]

Our rejection of such attitudes should not be mistaken for a belief that NOWS is not a medically consequential diagnosis or that being raised by a parent or within a family troubled with OUD does not pose serious risks. But these risks can be related to either a mother or father with a substance use disorder, and far less attention is paid to the need to drug test fathers before children are discharged into their care. Moreover, although screening can help anticipate and prepare for newborn infants who are at risk for NOWS (in addition to allowing treatment of women and, potentially,

families), screening will not, in general, prevent NOWS (except in the minority of cases in which medication-assisted withdrawal is undertaken). Although the medical argument for diagnosing children at risk is valid and strong, physicians must take care to ground policies in medical facts and not as a judgment against moral failings.

It may seem that the most straightforward way to diagnose all children at risk without allowing implicit bias to contaminate the process would be to perform testing of biologic specimens on all pregnant women. This approach has several drawbacks. In addition to limiting evaluation to a specific time point, a program of routine testing could undermine the mother's autonomy. Federal law requires states to have policies and procedures to notify child protective service of exposed newborn infants and to establish plans for safe care of such neonates. However, individual states vary regarding the definition of a "substance-exposed" neonate, when reporting should occur, and plans for safe care. Given the patchwork of laws regarding drug use in pregnancy, testing without consent could be both medically and socially perilous. It would be medically dangerous because, as ACOG has repeatedly pointed out,[143] it may discourage those women who are most in need of care from engaging with the health-care system. It would be socially perilous because of the quality of foster care in much of the United States. Finally, it could be interpreted to be a violation of the Fourth Amendment injunction against unreasonable search and seizure. If concern about the well-being of children is sufficient to obviate that constitutional protection, then laws could also require routine testing of surgeons, because any drug-related impairment of them certainly would pose a risk on par to that posed by a mother with a substance use disorder. Finally, if pregnant women as a group were stripped of that protection selectively, it may create a distinctive and lesser class of citizens with an attenuated relationship to the constitution and its guarantees. A federal appeals court already has litigated the appropriateness of that approach in Ferguson vs Charleston 2001 (in which the court used the term *drug screening*).[144] In a 6–3 ruling, the court said drug testing by a public hospital in Charleston, SC, violated the Fourth Amendment of the Constitution, which bars unreasonable search and seizure, even though the hospital's intent was to prevent women from harming their fetuses by using crack cocaine.

Thus, we argue that any protocol for the identification of drug-using pregnant women that relies on testing of biologic specimens as a first step, whether routinely or selectively, would be difficult to support on ethical grounds, unless patients received extensive, nondirective counseling that would likely be difficult to implement and document in a busy clinical setting. Screening with questionnaires may at first seem less ethically perilous, because it provides a reasonable guarantee of autonomy and because it would be difficult to compel a woman to answer a questionnaire or have her be unaware of what was being screened for. In addition, if a woman were required to complete a form, she could not be compelled to answer truthfully or fully. Furthermore, because the questionnaire would be uniform, it might seem that bias would not be an ethical barrier. However, just as in research, when studies must guard against performance bias as well as measurement bias, those who use questionnaire screening should evaluate their use for implementation bias. The body language or inflection of the person administering the questionnaire (assuming a computer-assisted self-interview is not used) could vary and could influence the type of answers given. The use of a validated tool would obviate concerns about differences in the way questions are posed ("when was the last time you used drugs?" vs "you don't use drugs do you?"); however, the use of a validated tool would not prevent the person being screened from answering untruthfully. For example, if a questionnaire is used in a jurisdiction that takes a more punitive approach to drug use in pregnancy, the proportion of truthful answers may be substantively lower than in a jurisdiction in which a medical model for addressing drug use is used. The testing attributes and the contents of the various screening tools are covered in the section "Screening and testing for substance abuse, including opioid use, in pregnancy," but regardless of which type of tool is chosen, its use will only pass ethical muster if it is linked to available medical care and treatment for those who screen positive. Moreover, when an initial screening questionnaire identifies patients who require follow-up questions and further conversation, providers, as part of those conversations, should discuss the reporting and other consequences of their responses. As already noted, when screening occurs in a setting focused on support and treatment rather than prosecution, it seems likely that patients will be more forthcoming and, consequently, more likely to receive care important to their own health, including the health of their pregnancy.

In summary, universal voluntary screening that uses questionnaire instruments when linked to appropriate services, and not biologic testing, is an ethical approach to the identification of women who are in need of substance use disorder care. It is also the approach supported by most professional organizations such as ACOG, the American Academy of Pediatrics, the American Medication Association, and the Centers for Disease Control and Prevention. It is not advocated by the US Preventative Services Task Force, but the reason is less reflective of ethical concerns than the standards it sets for proof that benefits outweigh burdens (ie, has the disease of interest been demonstrated to be ameliorated by the approach advocated).[145]

Given the potential dissonance between what ethics might suggest and what laws might mandate, what should a provider/patient champion do? What if a law requires that certain newborn infants have urine toxicology testing,

which is a test that effectively tests for substances a mother has used, or even requires testing of a mother's blood or urine directly? ACOG has proffered advice in that regard, recommending that physicians should advocate for patients by opposing coercive screening, testing, and treatments and by protecting patient autonomy and confidentiality ("to the extent allowable by laws"). ACOG goes on to recommend that providers should notify patients of mandated biologic testing and "make a reasonable effort to obtain informed consent." ACOG recommends that providers should work to create better laws and to retract punitive legislation, and they speak out in favor of evidence-based and consensual interventions. Finally, ACOG recommendations argue for providers to advocate for increased and evidence-based treatment and to support treatment, not prosecution, for these patients.[143] By engaging in these actions, health-care providers optimally will both serve their patients and uphold the highest standards of medical professionalism.

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