CME

Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes

Executive Summary of a Joint Workshop by the Eunice Kennedy Shriver *National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation*

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In April 2016, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development invited experts to a workshop to address numerous knowledge gaps and to review the evidence for the screening and management of opioid use in pregnancy and neonatal abstinence syndrome. The rising prevalence of opioid use in pregnancy has led to a concomitant dramatic five-fold increase in neonatal abstinence syndrome over the past decade. Experts from diverse disciplines addressed research gaps in the following areas: 1) optimal screening for opioid use in pregnancy; 2) complications of pregnancy associated with opioid use; 3) appropriate treatments for pregnant women with opioid use disorders; 4) the best approaches for detecting, treating, and managing newborns with neonatal abstinence syndrome; and 5) the long-term effects of prenatal opioid exposure on children. Workshop participants identified key scientific opportunities to advance the understanding of opioid use disorders in pregnancy and to improve outcomes for affected women, their children, and their families. This article provides a summary of the workshop presentations and discussions.

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See related editorial on page 7.

Opioid use has quadrupled over the past decade,[1] with 259 million prescriptions in 2012 alone in the United States, which consumes more prescription opioid pain relievers than any other nation.[2] Approximately one third of insured reproductive-aged women fill a prescription for an opioid medication

**For a list of invited speakers and participants, see Appendix 1, available online at http://links.lww.com/AOG/A951.*

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each year.[3] Every 3 minutes, a woman seeks care in an emergency department related to prescription opioid misuse.[1] Prescribed opioids that can be misused include codeine, fentanyl, morphine, opium, methadone, oxycodone, meperidine, hydromorphone, hydrocodone, propoxyphene, and buprenorphine.

Opioid use disorder is defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* as the repeated occurrence within a 12-month period of two or more of 11 problems, including: craving, tolerance, withdrawal, giving up important life events to use opioids, or an inability to cut down or control opioid use[4] (refer to Table 1 in Schuckit et al[5]).

The increasing prevalence of opioid use in pregnancy has led to a concomitant fivefold increase in neonatal abstinence syndrome over the past decade, from 1.2 to 5.8 per 1,000 hospital births.[6,7] Neonatal abstinence syndrome is a drug withdrawal syndrome that opioid-exposed neonates experience shortly after birth. Because abstinence is different from withdrawal, using the term "neonatal opioid withdrawal syndrome" may be more appropriate. A recent analysis from the state of Tennessee found that two thirds of neonatal abstinence syndrome cases were associated with legal prescriptions, and 28% of women enrolled in the state Medicaid program received at least one prescription for an opioid.[8] By 2012, nearly 22,000 neonates were born with neonatal abstinence syndrome in the United States each year, translating to one neonate born every 30 minutes and resulting in $1.5 billion in hospital charges nationwide.[6]

On April 4 and 5, 2016, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development convened a workshop entitled "Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes," cosponsored by the American College of Obstetricians and Gynecologists (the College), the American Academy of Pediatrics, the Society for Maternal-Fetal Medicine, the Centers for Disease Control and Prevention, and the March of Dimes, in which experts from diverse disciplines addressed research gaps in: 1) optimal screening for opioid use in pregnancy; 2) complications of pregnancy associated with opioid use; 3) the appropriate treatments for pregnant women with opioid use disorders; 4) the best approaches for detecting, treating, and managing newborns with neonatal abstinence syndrome; and 5) the long-term effects of prenatal opioid exposure on children. Workshop participants identified key scientific opportunities to advance the understanding of opioid use disorders in pregnancy to improve outcomes for affected women, their children, and their families.

MECHANISM OF OPIOID ADDICTION AND PHARMACOLOGY

Opioids bind to specific G-protein coupled receptors in the brain to produce a pleasurable sensation. After the first identification of the mu receptor in 1973,[9] delta, kappa, and nociceptin–orphanin FQ opioid receptors were identified. Opioids also depress respiration, potentially causing respiratory arrest and death. Opioid addiction is associated with compulsive drug-seeking behavior, physical dependence, and tolerance requiring higher doses to achieve the same physiologic effect. Inherited single nucleotide polymorphisms in the opioid receptor can reduce analgesia and potentially increase the likelihood of dependence.[10]

Once physical dependence has developed, withdrawal occurs if use is discontinued. For opioids with short half-lives such as heroin, withdrawal symptoms begin within hours after use and decrease greatly by day 4. For opioids with long half-lives such as methadone, withdrawal symptoms may not begin for several days and decrease at approximately day 10. Drug cravings may persist for years, thus leading to high rates of relapse.[5]

SCREENING FOR OPIOID USE DISORDER IN PREGNANCY

Pregnancy may be the only time that a woman presents for medical care and when an opioid use disorder can be identified and treated. There are concerns about screening only selected groups of women. Chasnoff et al[11] found that rates of drug use among pregnant women in a Florida county did not vary by race, but the rate at which women were reported to social services for drug use was 10 times higher in African Americans compared with other groups.

Use of a validated screening tool administered in a nondiscriminatory, routine, and voluntary system would be optimal. The College notes that: "Drug enforcement policies that deter women from seeking prenatal care are contrary to the welfare of the mother and fetus." Instead, they urge their members to identify and refer patients already misusing drugs to addiction treatment professionals.[12] Unfortunately, as of 2016, only 19 states had drug treatment programs specifically targeted to pregnant women, and only 12 provide pregnant women with priority access to state-funded drug treatment programs.[13]

Women have a number of reasons to not disclose substance use in pregnancy, including legal ramifications, child custody issues, and the stigma.[14] The fear

of consequences can actually discourage women from seeking prenatal care, placing both the mother and fetus at higher risk of complications.[15] Whereas screening for prenatal alcohol use is generally well-accepted, the validity, reliability, and clinical utility of standardized questionnaires to detect the use of illicit drugs during pregnancy have not been well established.[16]

There is disagreement between professional societies with regard to screening for substance use in pregnancy. The College recommends screening all women for substance use before and during early pregnancy and providing intervention when needed.[14] The U.S. Preventive Services Task Force has concluded that there is insufficient evidence to evaluate the benefits and harms of screening for illicit drug use in clinical populations including pregnant women.

Ideally, the experts at the workshop agreed that screening for substance use (alcohol, cigarette, illicit drugs, or prescription drugs without a prescription) during pregnancy should be universal. Women should be informed that these questions are asked of all pregnant women to ensure the mother and fetus receive the care they need and that the information will be kept confidential. Routine screening should rely on validated screening tools such as the 4Ps (copyrighted and has to be purchased) and CRAFFT questionnaires (Car, Relax, Alone, Forget, Friends, Trouble screen for women aged 26 years or younger) (refer to Box 1 in the College's Committee Opinion No. 524).[17] They can be used in direct interview format by physicians as well as nonphysicians and can be streamlined into clinical practice by using computer-based approaches. Direct face-to-face questioning often leads to greater discussion of treatment need and available resources.

Testing biomarkers associated with exposure is a second screening approach. Laboratory detection of substance use has significant advantages, including objectivity, ability to test for multiple substances, widespread availability, and well-established validity.[18,19] However, these tests may not be able to distinguish between occasional and regular use.[16] Furthermore, the short half-life of most substances and related metabolites limits urine detection to recent use only.[20] A negative test does not rule out substance use (especially if sporadic). False-positive tests can occur with devastating consequences to the woman. When testing for multiple substances, analysis of hair provides an extended window of detection[19]; but testing of damaged hair may be unreliable, and the cost is prohibitive for large-scale use. Urine testing has high specificity and positive predictive value depending on the assay and opioid drug being tested; it is relatively inexpensive, but sensitivity may be limited as a result of a short window of detection.[20]

The purpose of screening is to identify women with potential opioid use disorder and provide them appropriate care. Screening should be performed on a continuing basis, from the first prenatal visit to the puerperium. Laboratory testing is useful in conjunction with the interview and for referral into available treatment programs. Because biological assays are limited, awareness of the limitations of different assays is needed. Urine drug testing should be performed with the patient's consent and in compliance with existing state laws. Pregnant women should be informed of the potential consequences of a positive test before performing it, including any mandatory reporting requirements.[17]

MEDICATION-ASSISTED THERAPY

The effect of a comprehensive treatment plan for heroin addiction, including methadone maintenance and counseling for both patients and their partners, was first described in 1974.[21] The goals of treatment were to manage withdrawal, reduce cravings, and prevent illicit opioid use in the mother. Furthermore, in contrast to untreated heroin dependence, methadone treatment was associated with improved compliance with obstetric care; higher neonatal birth weights; lower rates of fetal growth restriction, abruptio placenta, preterm birth, fetal mortality, and neonatal death; and a greater chance of the neonate being discharged to his or her parents.[22–24] Zuspan et al[25] demonstrated in a single case with serial amniocentesis that low catecholamine levels in amniotic fluid during methadone treatment increased when the methadone dose was tapered, suggesting a fetal stress response with tapering. Together, these data led to the recommendation for medication-assisted treatment for all women during pregnancy and to avoid detoxification resulting from the high rates of relapse, extreme stress, and unknown harm to the fetus.[17,26]

Pregnant women can be initiated onto methadone either in a licensed outpatient methadone program[17] or as an inpatient. Methadone maintenance therapy, as prescribed and dispensed on a daily basis by a registered treatment program, is part of a comprehensive package of prenatal care, chemical dependency counseling, family therapy, nutritional education, and other medical and psychosocial services indicated for pregnant women with opioid use disorder. Once dose stabilization is achieved, patients continue to

receive medication daily at outpatient methadone treatment facilities.

Obstetricians should communicate with the addiction treatment program whenever there are concerns about a patient's care and methadone dosage. The dosage should be adjusted throughout pregnancy if needed, especially in the third trimester to avoid withdrawal symptoms, including drug cravings, abdominal cramps, nausea, insomnia, irritability, and anxiety.[27]

Studies have been inconsistent in establishing a relationship between methadone dose and the incidence, severity, or both of neonatal abstinence syndrome.[28–33] Methadone is usually initiated at 10–20 mg per day[34] and then titrated until the patient is asymptomatic in accordance with safe induction protocols (Table 1).[17,26,35–42] Nearly half of women require a low daily dose (less than 60 mg), and the remainder are maintained initially on a medium (60–89 mg) or high dose (greater than 90 mg).[27,35] As pregnancy advances, the dose of methadone usually increases rather than remaining stable (8%) or decreasing (7%).[27] Increased dosing during pregnancy is expected because of physiologic increases in maternal intravascular volume and renal elimination during the second and third trimesters. Pregnant women with rapid metabolism may need twice-daily dosing to optimally control their symptoms.[43,44] In a recent study, a mean methadone dose of 152 mg at delivery, divided into two to six doses per day, resulted in 92% of mothers being illicit drug-free at delivery and only 29% of neonates needing neonatal abstinence syndrome treatment.[45] An inadequate maternal methadone dosage may result in mild to moderate opioid withdrawal and cause fetal stress and increased likelihood for relapse.[46]

More recent evidence supports the use of buprenorphine for medication-assisted treatment during pregnancy. Buprenorphine is a partial mu opioid receptor agonist that binds to opioid receptors with

Table 1. Comparison of Methadone and Buprenorphine Use in Pregnancy

Characteristics	Methadone	Buprenorphine
Dosing	Directly observed therapy	Outpatient prescription Risk of diversion greater
1st dose	20 mg (oral) (range 15–30 mg)	2–4 mg (sublingual)
During withdrawal symptoms	5–10 mg every 3–6 h. Day 2: combined total of doses given in first 24 h	2 mg within 1–2 h
Dose increase interval	3 d	1 d
Dose	Initial maintenance: 69 mg (range 8–160 mg). At delivery: 93 mg (range 12–185 mg)	Maintenance dose range: 8–24 mg (beyond 32 mg, little increase in effect)
Half-life*	8–20 h	30 h
Polysubstance abuse	Preferred treatment for long-standing polysubstance abuse	May be more effective for prescription opioid users or new heroin users
Patient convenience	Less convenient—requires daily visits to federally licensed clinic. Take-home doses are allowed for Sundays or holidays unless random monthly urine drug screen is positive	More convenient—dispensed from office weekly or biweekly
Retention rates	Higher in treatment settings (78.1%)	Lower in treatment settings (57.7%)
Risk of overdose mortality	Higher, 4.18 /1,000 person-years in treatment	Lower, 0.98 deaths/1,000 person-years in treatment
NAS incidence†	Equal (57%)	Equal (47%)
NAS treatment duration	Longer (9.9 d)	Shorter (4.1 d)
Breastfeeding	Safe	Safe
Neurodevelopmental outcome of exposed children	No different from controls matched for age, race, and socioeconomic status	Limited evidence

NAS, neonatal abstinence syndrome.
* Reduced half-life as pregnancy advances.
† Not statistically different.

higher affinity but lower activity than complete agonists such as methadone and heroin. As a result of a decreased risk of overdose, buprenorphine inductions can occur in office-based settings prescribed by trained and approved physicians. This potentially increases the availability of treatment and decreases the stigma.[14,37] Buprenorphine is typically taken once or twice daily with an average dose of 10 mg.[47] Because it is a partial mu receptor agonist, buprenorphine has a ceiling effect at 32 mg, beyond which higher doses are not more effective.[26]

Buprenorphine improves neonatal outcomes compared with methadone therapy. The Maternal Opioid Treatment, Human Experimental Research study, a multicenter, randomized controlled trial that compared buprenorphine with methadone treatment, examined maternal and neonatal outcomes for 175 mother–child dyads. Buprenorphine-exposed neonates required 89% less morphine to treat neonatal abstinence syndrome and spent 43% less time in the hospital.[41] Maternal methadone was associated with a higher incidence of preterm labor and more respiratory distress in neonates at the time of delivery.[48] Furthermore, methadone-exposed neonates had higher neonatal abstinence syndrome scores[49] and required earlier treatment with morphine than buprenorphine-exposed neonates.[50] The total neonatal abstinence syndrome score and the individual signs of tremors, hyperactive Moro reflex, excessive irritability, and failure to thrive were significantly higher among methadone-exposed neonates than their buprenorphine-exposed counterparts.[49]

A meta-analysis compared 515 neonates whose mothers received methadone and 855 neonates whose mothers received buprenorphine in 12 studies. The unadjusted neonatal abstinence syndrome treatment risk was lower (risk ratio 0.90, 95% confidence interval [CI] 0.81–0.98) and mean length of hospital stay shorter (−7.23 days, 95% CI −10.64 to −3.83) in buprenorphine compared with methadone-exposed neonates. In treated neonates, neonatal abstinence syndrome treatment duration was shorter (−8.46 days, 95% CI −14.48 to −2.44) and total morphine dose was lower (−3.60 mg, 95% CI −7.26 to 0.07) in those exposed to buprenorphine. Buprenorphine-exposed neonates also had higher mean gestational age and greater weight, length, and head circumference at birth. Fewer women treated with buprenorphine used illicit opioids near delivery (risk ratio 0.44, 95% CI 0.28–0.70).[51]

The advantages of buprenorphine over methadone also include a lower risk of overdose[40] and the ability to be treated on an outpatient basis.[52] Disadvantages of buprenorphine compared with methadone include reports of hepatic dysfunction[26,36,53,54] (although recent reports do not support any adverse effects on the liver), lack of long-term data on infant and child outcomes (including adverse effects), a nonsignificant yet clinically important dropout rate resulting from dissatisfaction with the drug, or a more difficult induction with the potential risk of precipitated withdrawal.[55] Buprenorphine also has significant pharmacokinetic interactions with other drugs, including antiretroviral agents.[26,56] Lastly, compared with methadone programs, the less stringent structure of buprenorphine treatment may make it inappropriate for some patients who require more intensive counseling and supervision.[57]

Overall, these results support the use of buprenorphine as a potential first-line medication for opioid-dependent pregnant women who are new to treatment. Both the World Health Organization and the American Society of Addiction Medicine support methadone and buprenorphine as medication treatment options for pregnant women.[57,58] Practice guidelines for the use of buprenorphine during pregnancy are evolving; it is currently considered as a preferred treatment if a mother prefers buprenorphine to methadone, is willing to provide informed consent for treatment, and is capable of adhering safely to self-administration of the medication. Pregnant women on methadone maintenance therapy should not transition to buprenorphine, because buprenorphine may precipitate acute withdrawal.[58] The potential risk of unrecognized adverse long-term outcomes should be discussed with the patient. Methadone is the better option for women with long-standing, multisubstance abuse and previous failed attempts at detoxification.[35,37,58]

Buprenorphine is available as a single-agent product or in a combined formulation with naloxone, an opioid antagonist used to prevent diversion. Buprenorphine with naloxone is formulated to prevent injected use, because naloxone causes severe withdrawal symptoms when injected. During pregnancy, dosing with buprenorphine alone is recommended, although no maternal or neonatal adverse effects have been observed with use of the combination products.[59–62]

Naltrexone is a nonselective opioid receptor antagonist with potential to treat opioid use disorder in pregnancy by decreasing drug-seeking behaviors, drug cravings, and increasing treatment retention while eliminating the risk of neonatal abstinence syndrome.[63–65] However, limited data are available on the safety and efficacy of naltrexone during pregnancy.[66,67]

Interest has resurged in medically supervised withdrawal (ie, detoxification) during pregnancy to prevent neonatal abstinence syndrome. Recent reports

have described successful outcomes after medically supervised withdrawal during pregnancy in highly selected groups of women.[46,68–72] Each of these studies has limitations, including high relapse rates of 50% or greater, loss to follow-up, or both. If medically supervised withdrawal is attempted, it should be conducted under the supervision of a physician experienced in perinatal addiction treatment.[69] A recent retrospective analysis of detoxification during pregnancy in 301 women with opioid use disorder in Tennessee reported outcomes of four nonrandomized methods: acute detoxification of incarcerated patients (18.5% neonatal abstinence syndrome and 23.1% relapse rates); inpatient detoxification with intense outpatient follow-up (17.4% neonatal abstinence syndrome and 17.4% relapse rates); inpatient detoxification without intense outpatient follow-up (70.1% neonatal abstinence syndrome and 74.0% relapse rates); and slow outpatient buprenorphine detoxification (17.2% neonatal abstinence syndrome and 22.5% relapse rates).[72] Relapse was defined as a positive drug screen on admission, an admission by the patient at the time of delivery that she had relapsed, or a positive neonatal meconium test. It is important to note that neonatal abstinence syndrome is not the only outcome of interest, and it is unclear whether this approach is safe for the fetus, the mother, or both long term. Intense behavioral health support and follow-up were essential for success without opioid use.

Despite the fact that subsequent cohort studies have not found a significant risk of fetal loss associated with medically supervised withdrawal during pregnancy,[46,69] medication-assisted treatment is preferred over medically supervised withdrawal and is the standard of care for women with opioid use disorder in pregnancy. Medication-assisted treatment is associated with lower risks of maternal relapse to street drugs and improved compliance with prenatal care that outweigh the potential risks of neonatal abstinence syndrome.[17,46,57,58,66,73] A list of local treatment programs for opioid use disorder can be found at the Substance Abuse and Mental Health Services Administration's website (http://dpt2.samhsa.gov/treatment/directory.aspx).

PRENATAL CARE

Although observational studies suggest the possibility of an increase in relative risk for specific birth defects with opioid use (eg, congenital heart defects, neural tube defects, gastroschisis), the absolute risk is low.[74,75] Because these studies are limited by small sample size and confounding factors,[17,76] additional well-designed studies are needed. In a meta-analysis of three randomized controlled trials (n=223) and 15 observational studies (n=1,923) that compared buprenorphine and methadone treatment in pregnancy, no difference in the risk of congenital anomalies was identified. The authors concluded that the frequency and type of reported anomalies were similar to the general population with no particular patterns noted by treatment group.[76]

Special considerations for prenatal care in women with opioid use disorder are summarized in Box 1.[26,35,77–80] These women have high rates of co-occurring mental health disorders–mood disorders, anxiety, and posttraumatic stress disorder[81] as well as histories of physical and sexual abuse.[82] Polydrug use is common, and the effect of other potential drug–drug interactions on the fetus are poorly understood. Some of these women have poor nutrition, other chronic illnesses, and limited social supports. Finally, all of the characteristics detailed are associated with both poorer obstetric outcomes and addiction treatment outcomes. Hence, pregnant women with opioid use disorder have a unique set of needs and treatment must address those needs.

Many pregnant women with opioid use disorder receive little or no prenatal care,[83] often as a result of applicable local and state laws and regulations. Only 40% of publically funded treatment facilities provide any women-centered services, and the number that provide prenatal or postpartum care has decreased from 19% in 2002 to 15% in 2009 despite a dramatic increase in need.[84]

Peripartum Pain Management

Providing adequate analgesia to opioid-dependent patients during labor and delivery is challenging, because crosstolerance to the analgesic effects of opioids and opioid-induced hyperalgesia results in increased sensitivity to painful stimuli.[85,86] Special considerations for intrapartum care in women with opioid use disorders are summarized in Box 2. Studies show that women maintained on methadone or buprenorphine experience more pain after vaginal and cesarean delivery and require more opioid analgesia after cesarean delivery than women in a control group.[87,88] It can be particularly difficult to provide adequate analgesia for women on higher doses of buprenorphine because of its high affinity and partial agonist activity at the mu receptor. As a result, higher doses of full mu agonists are needed to displace buprenorphine, activate the receptor, and induce an analgesic effect.[86]

For labor analgesia, opioid dependence will not affect the efficacy of local anesthetics. Thus, epidural anesthesia or combined spinal–epidural analgesia often provides adequate pain relief. However, modern epidural analgesia generally includes low concentrations

Box 1. Prenatal Care for Women With Opioid Use Disorder

Prenatal Counseling Regarding Risks

- Birth defects: absolute risk is low—some evidence for increased risk in studies with small sample sizes and potential confounding
- Fetal growth restriction: increased risk of association based on strong evidence
- Preterm birth: increased risk of association based on strong evidence

Comorbid Conditions Screening

- Screen or test for:
  - Chronic pain conditions
  - Sexually transmitted infections
  - Infectious diseases (human immunodeficiency virus, hepatitis B, and hepatitis C at initial visit and repeated in the third trimester, if indicated)
  - Liver function tests
  - Electrocardiogram before starting methadone (causes prolongation in QT interval)
- Concomitant medications (selective serotonin reuptake inhibitors, benzodiazepines, antipsychotics)
- Multisubstance use (alcohol, tobacco, marijuana)

Psychosocial Care

- Comprehensive assessment of mental health, screening for posttraumatic stress disorder, depression, anxiety, bipolar disease, other psychiatric disorders
- Social conditions (intimate personal violence, unstable housing, lack of social support, partner use, food insecurity, employment, education, parenting, legal issues)
- Residential treatment

Obstetrician–Gynecologist Prenatal Care

- Antenatal testing only if other clinical indication arises; eg, fetal growth restriction—lack of evidence for need for opioid use disorder alone
  - Perform at least 4–6 hours after the woman takes her daily maintenance methadone dose (reduce false-positive rate of nonreactive nonstress test or nonreassuring biophysical profile)
- Ultrasound screening
  - 18–20 weeks of gestation anatomy ultrasonogram
  - Serial fetal growth assessment
- Multispecialty prenatal care needed
  - Anesthesia consult
  - Neonatology or pediatrics consult

of local anesthetics (to minimize motor blockade) and short-acting opioids (eg, fentanyl). Opioids are not fully effective in opioid-dependent patients, which may diminish the effectiveness of epidural analgesia in some patients. Solutions with higher concentrations of local anesthetics or other nonopioid adjuvants (eg, clonidine) may be necessary to achieve adequate analgesia. Patients who are unable to tolerate neuraxial anesthesia can be treated with short-acting opioids titrated to effect. It is important to avoid treating opioid-dependent patients with mixed antagonists and agonists (eg, nalbuphine or butorphanol), which are widely used for analgesia and pruritus, because these can precipitate withdrawal.[17,26,89,90]

Adequate analgesia after vaginal delivery can generally be achieved with nonsteroidal anti-inflammatory drugs and acetaminophen in combination with opioid maintenance therapy. However, acetaminophen is contraindicated in those with hepatitis C, which could affect up to 30% of opioid-dependent women.[48] Clinical protocols for nonnarcotic pain management after delivery and discharge should include ice packs and analgesic creams.

For cesarean delivery, neuraxial anesthesia (ie, spinal or epidural or combined spinal–epidural) is preferred. Postoperative pain control can be problematic. Intrathecal or epidural opioids can be administered, although they may not be fully effective for

Box 2. Intrapartum and Postpartum Care for Women With Opioid Use Disorder

Pain Management Intrapartum

- Train labor and delivery and postpartum staff in appropriate pain control
- Doula may be helpful, if available
- Medication-assisted treatment: continue maintenance dosing during hospitalization
- Medications
  - Avoid mixed antagonist and agonist narcotics (eg, butorphanol, nalbuphine, and pentazocine)
  - Early epidural
  - Neuraxial anesthesia
- Alternative pain management
  - Mindfulness training, relaxation training
  - Gabapentin, ketamine, transversus abdominis plane blocks
  - Nitrous oxide

Postoperative Pain Management

- Cesarean delivery: patient-controlled analgesia; scheduled regimen of nonsteroidal anti-inflammatory drugs or acetaminophen
- Vaginal delivery: nonsteroidal anti-inflammatory drugs and topical analgesics preferred
- Judicious prescribing of short-acting opioids post-cesarean delivery, short follow-up
- Anxiety management: be cautious with coadministration of benzodiazepines, because this can lead to respiratory depression
- Avoid trigger medications (eg, oxycodone) postpartum

Postpartum Support

- Allied health professionals may be used to provide in-depth, consistent follow-up
- Storage and disposal of leftover opioid medicine
- Social services consultation: assess custodial care for the newborn and other children
- Contraception counseling: encourage long-acting reversible contraception
- Lactation counseling to encourage and support breastfeeding

postoperative pain. Patient-controlled analgesia can be used and titrated to effect with higher than usual doses required. Nonsteroidal anti-inflammatory drugs and acetaminophen should be used. Use of gabapentin, transversus abdominis plane blocks, and intravenous acetaminophen may be opioid-sparing approaches that have utility in this setting, but more data are needed.

Generally, methadone should be continued at the usual dose throughout the peripartum period to avoid withdrawal. By the sixth postpartum week, 85% of patients remain within 10 mg of their methadone dose at delivery.[27] For buprenorphine, commonly used approaches include continuing buprenorphine at the usual dose throughout the peripartum period; discontinuing buprenorphine at the time of admission to labor and delivery (particularly for planned cesarean deliveries) and substituting with either long-acting (eg, MS Contin or fentanyl patch) or short-acting opioids (eg, immediate-release oxycodone or hydrocodone); or administering buprenorphine in divided doses (every 6 hours at 25% of maintenance dose to maximize the analgesic effects).[34,37,85,86]

The postpartum patient who receives opioid therapy should be closely monitored for symptoms of oversedation with dosages titrated as indicated. Other medications that can produce sedation (eg, benzodiazepines and zolpidem) should be avoided to decrease the risk of respiratory depression.[85,91] Data from nonpregnant women suggest treatment of acute postsurgical pain for patients on methadone therapy is not a risk factor for relapse.[86,92] However, it is prudent to avoid "triggering" opioids (eg, oxycodone), provide close follow-up, prescribe very limited quantities, and rapidly taper opioids by adding nonopioid alternatives. It is also reasonable to select opioids with the least euphoric potential for the treatment of acute pain.[93]

Lastly, of concern is the exposure of opioid-naive patients to opioid medication after cesarean delivery. A recent survey of 667 postcesarean patients conducted at six U.S. centers found that a median of 40 tablets was dispensed and 20 tablets were consumed.[94] Of those with leftover opioids, 93.2% had not disposed of the excess medication. This suggests that the amount of opioids prescribed after cesarean delivery generally exceeds the amount consumed by a significant margin and represents an important area of overprescribing. Recent data also suggest 1 in 300 opioid-naive patients exposed to opioids after cesarean delivery go on to become persistent users.[95]

POSTPARTUM CARE

Stresses associated with motherhood, newborn care, breastfeeding, and sleep deprivation can be overwhelming for patients with limited social support and resource availability, especially when infants are more irritable from neonatal abstinence syndrome.[96] Therefore, interventions designed to 1) improve rates and duration of breastfeeding; 2) increase the use of hormonal and long-acting reversible contraceptive methods; and 3) identify and treat postpartum depression are necessary to improve outcomes for women with opioid use disorder. Special considerations for

postpartum care in affected women are summarized in Box 2.

Breastfeeding is particularly important for women with an opioid use disorder and their newborns, because it is associated with decreased severity of neonatal abstinence syndrome, increased maternal confidence, stress reduction, and enhanced maternal–child bonding.[97–100] Compared with formula-fed infants, breastfed infants are less likely to need pharmacologic treatment for neonatal abstinence syndrome. If treatment is required, breastfed infants require lower doses of morphine and thus have shorter hospital lengths of stay.[101–104] Breastfeeding may also enhance compliance with medication-assisted treatment and be protective against illicit drug use.[98] The American Academy of Pediatrics recommends breastfeeding for women taking methadone or buprenorphine, regardless of maternal dose because very little methadone (1–3% of the maternal weight-adjusted dose) and minimal buprenorphine (less than 1% of the maternal weight-adjusted dose) is present in breast milk.[98–100,105–107]

Despite recommendations, breastfeeding rates among women on methadone range from 24% to 46% and as many as 60% of those who initiate breastfeeding stop after 6 days.[108,109] In contrast, breastfeeding initiation rates reach 76% in women on buprenorphine with 66% still breastfeeding at 6–8 weeks postpartum.[110] As a result of significantly improved maternal and neonatal outcomes, women adherent to methadone or buprenorphine maintenance treatment should be encouraged to breastfeed unless there are specific reasons not to do so (eg, human immunodeficiency virus infection, other illicit drug use).[99,100,107,111,112]

Over 86% of pregnancies conceived by women with opioid use disorder are unintended compared with 31–47% of pregnancies in the general population.[113,114] Women also report higher pregnancy rates with 29% reporting six or more pregnancies and 6% reporting 10 or more pregnancies.[114] A lack of awareness about available family planning services, mistrust of health care providers, ongoing illicit drug use, and lack of transportation and child care create significant barriers to accessing family planning services.[115,116] In evaluations of contraceptive use, 25–75% of sexually active women with an opioid use disorder reported no contraceptive use.[117–120] Even among women using contraception, approximately two thirds of women report using condoms.[114,119,120]

Highly effective postpartum contraception is critical to avoiding unintended pregnancy. Long-acting reversible contraception such as intrauterine devices and subdermal implants effectively prevent unintended pregnancies and should be promoted over alternative methods as a result of enhanced compliance.[120–122] Use among women with opioid use disorder ranges from 2% to 29%.[120] Long-acting reversible contraception insertion in the immediate postpartum period, before patient discharge after delivery, should be considered to reduce barriers such as poor compliance with the postpartum visit.[123,124] Efforts to incorporate comprehensive family planning services for women and their partners into opioid use disorder treatment programs are also desirable.

Access to adequate postpartum psychosocial support services, including chemical dependency treatment and relapse prevention programs, should be ensured. The prevalence of anxiety and depression in pregnant women with an opioid use disorder range from 65% to 73% and more than 12% of women report suicidal thoughts.[81,125] Women who report psychiatric symptoms often have greater addiction severity, are more likely to have deficits in family and social functioning, and are more likely to discontinue opioid use disorder treatment programs.[81,126] Poor social support, low income, and education further place pregnant women with an opioid use disorder at significant risk for postpartum depression.[127] Incorporation of perinatal psychiatric screening and treatment within opioid use disorder treatment program settings are needed.

NEONATAL ABSTINENCE SYNDROME AND CHILD HEALTH OUTCOMES

In the 1970s, neonatal signs of withdrawal from methadone were reported as neonatal abstinence syndrome. In the mid-1970s, Finnegan et al[128] and Lipsitz and Blatman[129] published their individual neonatal abstinence syndrome scoring systems, which are still routinely used today. Subsequently, withdrawal from buprenorphine and OxyContin were reported in 1997 and 2002, respectively. Both licit (prescription of opioid-containing pain relievers) and illicit (eg, heroin) maternal opioid use as well as the use of maternal medication-assisted treatment put neonates at risk for developing neonatal abstinence syndrome. In neonates exposed to methadone, signs of neonatal abstinence syndrome usually appear within 3–5 days of birth, but may appear as late as a week of age and last from days to weeks and rarely months of life. Neonates exposed to buprenorphine who develop neonatal abstinence syndrome generally develop symptoms by 48 hours of life, peaking at 72–96 hours.[49]

Neonatal abstinence syndrome is characterized by hyperactivity of the central and autonomic nervous systems. Individual signs include dysfunction in the

central nervous system (irritability, high-pitched cry, tremors, hypertonia, hyperreflexia, sleep disturbances); gastrointestinal system (regurgitation, loose stools, dysrhythmic sucking and swallowing, poor feeding, weight loss); respiratory system (tachypnea); and the autonomic nervous system (sweating, sneezing, yawning, nasal stuffiness, hyperthermia).

Assessment should consider the spectrum of neonatal abstinence syndrome signs that describe how the neonate functions in each specific neurobehavioral domain, that is, from no signs or dysregulated behavior to mild, moderate, and severe dysregulation.[130] Optimal assessment should involve examination of the overall neurobehavioral functioning of the neonate. Different substances (eg, psychotropic medications, other illicit drugs) may have their own withdrawal syndrome, can potentiate opioid-induced neonatal abstinence syndrome, or both. There is currently no method to assess the effect of other psychoactive substances on neonatal abstinence syndrome, because scoring tools are designed primarily for opioid-exposed neonates.

All neonates born to women who use opioids during pregnancy should be monitored for symptoms of neonatal abstinence syndrome for at least 5 days to determine whether they are exhibiting signs significant enough to require treatment.[131] It is essential to identify the opioid-exposed mother–neonate dyad antenatally or soon after birth to prevent early hospital discharge, promote breastfeeding (if safe to do so), assess the need for nonpharmacologic interventions (swaddling, rooming in), observe for the need for pharmacotherapy, and coordinate necessary help for the mother. Using a scoring system to assess neonatal abstinence syndrome is most efficient and feasible in a busy clinical setting. There have been six Neonatal Abstinence Scores published between 1975 and 2009: The Finnegan Neonatal Abstinence Scoring Tool in 1975[128]; the Neonatal Drug Withdrawal Scoring System in 1975[129]; Ostrea Tool in 1975[132]; the Neonatal Narcotic Withdrawal Index in 1981[133]; the Neonatal Withdrawal Inventory in 1988[134]; and the Maternal Opioid Treatment: Human Experimental Research Study Score (modified Finnegan).[135] Specific recommendations on their use are available for some scores with instructions to assure interrater reliability. The key issues in scoring should be decide on which score to use; have a protocol on how to administer it; and provide continuous training to assure interrater reliability. There are ongoing studies designed to simplify the application of the Finnegan scoring system as well as developing alternative physiologic assessments that may more accurately define when an neonate with neonatal abstinence syndrome requires treatment and can wean off that treatment.

Not all neonates exposed to antenatal opioids will develop significant signs of withdrawal. Environmental factors can certainly increase the incidence and severity of neonatal abstinence syndrome. These include exposure to central nervous system active agents such as nicotine in cigarette smoke, benzodiazepines, gabapentin, selective serotonin reuptake inhibitors, and marijuana.[8,136] There is also some evidence to indicate that genetic and epigenetic factors also affect neonatal abstinence syndrome severity in some neonates.[137,138] Further studies are needed to better define the genetic–epigenetic and the environmental risk factors that contribute to the incidence and severity of neonatal abstinence syndrome.

Optimal assessment of the neonate with neonatal abstinence syndrome has not been definitively established. Current tools are subjective in nature and are designed for opioid-exposed neonates born at term. They do not apply well to preterm neonates, older neonates, or polysubstance-exposed neonates. Neonatal assessment should also include an assessment of the mother–caregiver and the environment, which is not standard today. Appropriate neurobehavioral or nonpharmacologic interventions may reduce the severity of neonatal abstinence syndrome by decreasing neonatal stress and promoting neonatal self-regulation and development.[139] These interventions should be instituted before the initiation of drug treatment and may be successful in avoiding the need for pharmacologic therapy. The neonate with neonatal abstinence syndrome is best managed in a calm environment (not guaranteed in a busy neonatal intensive care unit) by specially trained personnel. Scoring systems that are used to decide whether a neonate requires pharmacotherapy may not accurately reflect the neonate's functioning and regulatory capacity. A comprehensive understanding of the neonate is necessary for the optimal treatment of neonatal abstinence syndrome, that is, to decrease sensory overload, mitigate irritability, minimize uncontrolled body movements, and address specific problems with sleep, feeding, and interaction.[140]

The incidence and the treatment of neonatal abstinence syndrome have a high level of variability (depending on multiple factors), with up to 80% of opioid-exposed neonates in some studies requiring pharmacologic interventions.[141] Neonatal care is summarized in Box 3. Opioid medications are recommended when the neonatal abstinence syndrome score reaches a moderate level and the neonate cannot be

managed by supportive measures alone.[131] Once treatment is initiated, adherence of all health care providers to a standardized protocol appears to improve treatment outcomes (length of hospital stay, duration of pharmacologic treatment, cumulative dose, and number of treatment drugs) more than the choice of drug or the specific treatment protocol.[142] Based on published data through 2012, the American Academy of Pediatrics recommends commencing pharmacologic treatment with oral morphine or methadone, with preservative-free formulations recommended. However, the optimal initial drug of choice remains unknown and is currently under study. When a neonate reaches a maximal dose of a first-line medication, a second-line medication (eg, phenobarbital or clonidine) is typically added. Just as first-line medications and dosing have not been well studied, second-line drugs have even less data to support their use.

Rational pharmacotherapy should use the minimum dose of drug necessary to achieve treatment

Box 3. Neonatal Care for Children of Women With Opioid Use Disorder

Assessment for Neonatal Abstinence Syndrome

- Scoring tools
  - Optimal assessment for neonates with neonatal abstinence syndrome has not been defined
  - Tools are subjective or highly variable
- Assessment period
  - Optimal timing of assessments as fewer symptoms in the first 24–96 hours
  - Depends on opioid metabolism and potential drug–drug interactions (polypharmacy)
  - Late onset possible (eg, 2 weeks)—uncommon but does exist
  - Rooming-in and more direct family involvement compared with remaining in the nursery for more continuous observation and assessment
- Factors affecting development and severity of neonatal abstinence syndrome
  - Gestational age—preterm compared with term; birth weight
  - Methadone compared with buprenorphine—variability in pharmacokinetics and pharmacodynamics in neonates
  - Rooming in which promotes kangaroo care and breastfeeding
  - Tobacco smoking
  - Benzodiazepine exposure
  - Selective serotonin reuptake inhibitor exposure
  - Genetic predisposition

Treatment of Neonatal Abstinence Syndrome

- Need to standardize protocols and establish best practices (standard of care)
- Individualized to the neonate and mother, hospital, home environment, or all
- Input from social services for predischarge and postdischarge treatment and follow-up
- Optimal pharmacologic approach unknown, but opioids recommended as first-line drugs
- When maximal dose achieved (which has not been well established) without control of symptoms, a second- or even third-line agent may be needed (clonidine, phenobarbital)
  - Some medications contain alcohol and other preservatives with potential toxicities
  - Goal of treatment—adequate sleep, feeding, weight gain, and physiologic functions
- Need staffing requirements studies (day-to-day care, staff ratios, rooming-in)

Neonatal Discharge and Follow-up

- Best place and environment for neonates with neonatal abstinence syndrome
  - Create programs that work with the mother–neonate dyad, especially if the mother is in a substance abuse treatment postpartum
  - Regional variability in resources, requirements, and populations
- Educate parents (mothers and fathers) in special needs for neonates with neonatal abstinence syndrome
- Home weaning protocols and follow-up
  - 10% of neonates discharged on phenobarbital for prolonged periods of time
  - High variability in weaning; lack standard monitoring and dosing changes
  - More likely to be rehospitalized—coordinate services to avoid it

Box 4. Research Gaps and Opportunities

Basic Science

- Opioid use disorder is a syndrome commonly associated with multiple potentially deleterious exposures other than opiates and several adverse pregnancy outcomes including poor fetal growth, preterm birth, fetal loss, stillbirths and birth defects
  - It is unlikely that the associated adverse pregnancy outcomes will be scientifically rigorously attributable to individual exposures among the numerous exposures that are characteristic of the syndrome
  - Many covariates (exposures) that are strongly associated with opiate use include tobacco, alcohol, benzodiazepines, cocaine and other substances of abuse, poor nutrition, anemia, sexually transmitted infections, unplanned and undesired pregnancies, poor educational attainment, low socioeconomic status, poor housing conditions, exposure to and legitimate fear of violence
  - Absent scientifically rigorous data on causation, how should potentially deleterious exposures be prioritized for interventions?
  - Are there undiscovered mechanisms of adverse biological effects on placental function of potentially deleterious exposures?
- What are the developmental and inherited genetic variations in opioid action and metabolism?

Prenatal Screening for Opioid Use Disorder

- What is the best method for screening?
  - Modality (computer questionnaire, in-person interview [with whom], biological sample)
  - Optimal time, interval, and frequency
  - Optimal tool
  - What are the barriers to screening (real and perceived)?
- How to maintain confidentiality and trust while minimizing judgmental behavior and punitive implications

Obstetrics and Gynecology Prenatal Care

- How best to structure comprehensive care to bring all resources to women
- What is the optimal assessment for fetal well-being?

Medication-Assisted Treatment and Detoxification

- What is the best technique to engage women in treatment?
  - Include women recovering from opioid use disorders?
  - Develop a screening tool to predict probability of relapse
  - Will physiologic measures of opioid withdrawal be more useful than simply assessing cravings?
- What are the optimal safety, efficacy, and treatment approaches during pregnancy?
  - Methadone compared with buprenorphine
  - Combinations (buprenorphine+naloxone, naloxone, or naltrexone)
  - Effect of other agents (eg, psychotropic medications, "mood stabilizers")
- Can "precision medicine" inform the appropriate dosing for all medications throughout pregnancy? Postpartum? During breastfeeding?
  - Which medication works best for which patients?
  - Need pharmacokinetic and pharmacodynamic studies for all medications during pregnancy and with breastfeeding
  - Need test for mother's metabolism (fast compared with slow metabolizers)—may need different dosing schedules
- How long do patients need medication? What is the best way to wean them?
- Is there a subgroup of women with opioid use disorder who will be successful with detoxification therapy?
  - Can we reliably identify them a priori?
  - Need evidence for optimal fetal assessment and efficacy in this scenario
  - Role of benzodiazepines and adjunct medications (eg, adrenergic blockade) with respect to success
  - Need medical interventions for known consequences of detoxification
  - Need trials of opioid detoxification with fetal monitoring and excellent follow-up analyzed by intent to treat
  - Anticipate and minimize potential relapse rates if detoxification is undertaken
- Understand the pathophysiology of detoxification during pregnancy: maternal, uteroplacental function, and fetal effects

(*continued*)

Box 4. Research Gaps and Opportunities (*continued*)

Pain Management Intrapartum

- Optimal and appropriate agonist dosing
  - Integration of narcotic and nonnarcotic medications
  - Effect modifiers (eg, polydrug use, smoking, and stress)

Pain Management Postoperative

- Comparative effectiveness of nonopioid alternatives for postcesarean pain control (eg, gabapentin, transversus abdominis plane block, intravenous acetaminophen)
- Education and changing physician practices in postpartum pain management
- What is the risk of overdose in those using illicit opioids or on high-dose chronic opioid therapy?
  - Is pregnancy an independent risk factor for overdose? If so, is it mediated by sleep-disordered breathing?
- Postcesarean opioid use: how to align the amount of opioid medication prescribed with what is needed; implications for relapse

Postpartum Care and Support

- Comparative effectiveness and safety of buprenorphine management strategies after delivery
  - Continuing buprenorphine or replacing it with pure μ agonists
- Preventing postpartum relapse
  - What are the risk factors for relapse after delivery?
  - Do opioid type, dosing, and management strategies affect risk of relapse?
- Breastfeeding
  - Improve prenatal education and counseling of the benefits of breastfeeding
  - What interventions could increase breastfeeding initiation rates and prolong breastfeeding duration?
  - What are the causal pathways between breastfeeding and the decreased occurrence and severity of neonatal abstinence syndrome?
- Contraception
  - How to improve access, availability, acceptance, and affordability of long-acting reversible contraception
  - How to increase regular dual use of condoms and nonbarrier methods to prevent sexually transmitted infections
- Postpartum depression
  - What factors correlate with development of postpartum depression?
  - What are the best depression screening tools for women with substance use disorder, including frequency and timing of screening in prenatal and postpartum periods?
  - Who should be treated prophylactically to prevent postpartum depression?

Neonatal Screening and Assessment for Neonatal Abstinence Syndrome

- What are the best methods for identification and screening for neonatal abstinence syndrome?
  - Need biomarker for neonatal abstinence syndrome as a physiologic state, for example, epinephrine or cortisol levels for neonatal abstinence syndrome
  - Need laboratory-on-a-chip method for rapid testing for neonatal abstinence syndrome
  - What are the predictive factors for development of neonatal abstinence syndrome? Diagnostic assays for who will develop neonatal abstinence syndrome and how they will respond to therapies
- What is the best method for assessing development of neonates with neonatal abstinence syndrome?
  - What factors most accurately define the appropriate observation period for neonates at risk for neonatal abstinence syndrome? How often should neonates be evaluated?
  - Develop objective tools using technology-assisted assessment
  - Individualized, comprehensive assessment to identify those neonates most susceptible to poor developmental outcomes that considers:
    a. Neonatal state
    b. Genetic and epigenetic information
    c. Pharmacologic management
    d. Neurobehavioral functioning
    e. Soothing techniques to avoid pharmacotherapy when possible
    f. Environment
    g. Adaptable for neonatal gestational and developmental age

(*continued*)

Box 4. Research Gaps and Opportunities (*continued*)

- Test scoring systems and assessment protocols against each other
- What factors affect risk profiles for neonates? Different substance exposures may lead to the same symptoms; need ability to distinguish them to determine best therapy.
  - Population heterogeneity
  - Dose and gestational age of exposure to maternal opioids

Treatment of Neonatal Abstinence Syndrome

- What is the optimal initial drug for treatment of neonatal abstinence syndrome?
- What are appropriate indications for a second drug?
- Can genetic or epigenetic analyses be combined with antenatal exposures to tailor an optimal treatment regimen?
- What is the role of polydrug use?
- What criteria best select neonates and families for outpatient management?
- What resources are needed for safe and effective outpatient management?

Neonatal Discharge and Follow-up

- What are the longer-term development outcomes for children prenatally exposed to agonist or antagonist medications?
  - Exposure is different based on variations in neonatal metabolism
  - No data on exposure timing and long-term developmental outcomes
  - Role of the environment is critical to outcome
  - Latent effects
- How do maternal psychiatric comorbidities and propensity for substance abuse affect child outcomes?
- What are the barriers to care related to state regulations?
- Do state-specific regulations affect screening, treatment, and neonatal outcomes?

goals. Treatment is often initiated based on the weight of the neonate, the severity of symptoms, or optimally a combination of both. Steady-state drug levels are needed to achieve the desired treatment effect and are a function of the dose, dosing interval, and half-life of the drug. It may be appropriate to use a loading dose or administer additional doses at the start of treatment to achieve a steady-state level more rapidly rather than increasing the daily dose if a neonate does not respond in a timely fashion. It is important to subscribe to the principle that the goal of therapy is not to generate very low neonatal abstinence syndrome scores, because the risk–benefit ratio of this approach has not been established. Treatment is considered adequate if the neonate has rhythmic feeding and sleep cycles and optimal weight gain. Comprehensive treatment goals are fourfold: 1) support vital neonatal functions and development (nutrition, sleep, social interaction); 2) initiate family bonding (integrated care, breastfeeding if possible); 3) prevent complications (dehydration, weight loss, skin breakdown, inadequate rest, central nervous system hyperactivity, seizures); and 4) educate the family and provide adequate medical and social resources for the neonate and family after discharge, because some neonates will still be irritable and have increased needs despite being weaned off medical therapy.

There is a lack of evidence on the long-term effects of prenatal opioid exposure. Most studies were conducted before the start of the current opioid epidemic and have not included addiction related to prescription drug use. In addition, the long-term outcome of children with neonatal abstinence syndrome is virtually unknown because these children typically were embedded within more general studies of children with in utero opioid exposure and most studies followed children for only a few years. In general, findings from the follow-up literature on children with prenatal opioid exposure are inconsistent.[42] For example, earlier studies have not found significant differences in cognitive development between children exposed to methadone in utero when followed to 5 years of age compared with control groups matched for age, race, and socioeconomic status. However, scores were often lower in both groups compared with data from the general population. In other studies, a number of cognitive, motor, and behavioral deficits were identified such as lower IQ scores and poor social skills. Sample sizes were small and thus could not account for multiple confounding factors such as polydrug use, environmental exposures, and poverty. Participant retention rates were poor, and identifying

appropriate comparison groups was problematic. In a meta-analysis, only five studies were identified that reported quantitative effects of prenatal opioid exposure on child neurobehavioral outcome.[143] Preventive interventions that focus on enriching the early experiences of such children and improving the quality of the home environment are likely to be beneficial.

DISCUSSION

A coordinated, multisystem approach best serves the needs of pregnant women with opioid use disorders and their newborns. Key knowledge gaps have been identified, with additional research needed to improve outcomes for women with opioid use disorder and for their children (Box 4. Obstetric research is needed that focuses on optimal screening, treatment, and care throughout pregnancy and the postpartum period as well as elective maternal medically supervised withdrawal during pregnancy. Neonatal focused research needed includes 1) a new scoring tool that incorporates a neurobehavioral assessment of the substance-exposed neonate's functioning as well as the need for pharmacologic management; and 2) optimal approaches to nonpharmacologic and pharmacologic therapy when needed. There are extremely limited data on childhood outcomes; well-designed studies accounting for the complexity of in utero and postnatal exposures are urgently needed. Additionally, basic science research using animal models of prenatal opioid exposure are useful to identify potential neurodevelopmental consequences after in utero exposure. Research to understand the genetic and epigenetic predisposition to tailor prevention and treatment interventions is needed. Lastly, training of health care providers in a manner that fosters multidisciplinary care and crosses specialty area boundaries is needed to provide optimal care to pregnant women with opioid use disorders and their children.

REFERENCES

1. Centers for Disease Control and Prevention. Vital signs: prescription painkiller overdoses: a growing epidemic, especially among women. Available at: http://www.cdc.gov/vitalsigns/prescriptionpainkilleroverdoses/. Retrieved October 11, 2016.
2. International Narcotics Control Board. Report of the International Narcotics Control Board for 2010. New York (NY): United Nations; 2010.
3. Ailes EC, Dawson AL, Lind JN, Gilboa SM, Frey MT, Broussard CS, et al. Opioid prescription claims among women of reproductive age–United States, 2008–2012. MMWR Morb Mortal Wkly Rep 2015;64:37–41.
4. American Psychiatric Association, DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Arlington (VA): American Psychiatric Association; 2013.
5. Schuckit MA. Treatment of opioid-use disorders. N Engl J Med 2016;375:357–68.
6. Patrick SW, Davis MM, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. J Perinatol 2015;35:667.
7. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000–2009. JAMA 2012;307:1934–40.
8. Patrick SW, Dudley J, Martin PR, Harrell FE, Warren MD, Hartmann KE, et al. Prescription opioid epidemic and infant outcomes. Pediatrics 2015;135:842–50.
9. Pert CB, Pasternak G, Snyder SH. Opiate agonists and antagonists discriminated by receptor binding in brain. Science 1973;182:1359–61.
10. Campa D, Gioia A, Tomei A, Poli P, Barale R. Association of ABCB1/MDR1 and OPRM1 gene polymorphisms with morphine pain relief. Clin Pharmacol Ther 2008;83:559–66.
11. Chasnoff IJ, Landress HJ, Barrett ME. The prevalence of illicit-drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County, Florida. N Engl J Med 1990;322:1202–6.
12. Substance abuse reporting and pregnancy: the role of the obstetrician-gynecologist. Committee Opinion No. 473. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;117:200–1.
13. Guttmacher Institute. State laws and policies: substance abuse during pregnancy. Available at: https://www.guttmacher.org/state-policy/explore/substance-abuse-during-pregnancy. Retrieved September 21, 2016.
14. Alcohol abuse and other substance use disorders: ethical issues in obstetric and gynecologic practice. Committee Opinion No. 633. American College of Obstetrician and Gynecologists. Obstet Gynecol 2015;125:1529–37.
15. El-Mohandes A, Herman AA, Nabil El-Khorazaty M, Katta PS, White D, Grylack L. Prenatal care reduces the impact of illicit drug use on perinatal outcomes. J Perinatol 2003;23:354–60.
16. U.S. Preventive Services Task Force. Final recommendation statement: drug use, illicit: screening. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/drug-use-illicit-screening. Retrieved September 21, 2016.
17. Opioid abuse, dependence, and addiction in pregnancy. Committee Opinion No. 524. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;119:1070–6.
18. Wolff K, Farrell M, Marsden J, Monteiro MG, Ali R, Welch S, et al. A review of biological indicators of illicit drug use, practical considerations and clinical usefulness. Addiction 1999;94:1279–98.
19. Strano-Rossi S. Methods used to detect drug abuse in pregnancy: a brief review. Drug Alcohol Depend 1999;53:257–71.
20. Yonkers KA, Howell HB, Gotman N, Rounsaville BJ. Self-report of illicit substance use versus urine toxicology results from at-risk pregnant women. J Subst Use 2011;16:372–389.
21. Harper RG, Solish GI, Purow HM, Sang E, Panepinto WC. The effect of a methadone treatment program upon pregnant heroin addicts and their newborn infants. Pediatrics 1974;54:300–5.
22. Kandall SR, Albin S, Gartner LM, Lee KS, Eidelman A, Lowinson J. The narcotic-dependent mother: fetal and neonatal consequences. Early Hum Dev 1977;1:159–69.

23. Kaltenbach K, Berghella V, Finnegan L. Opioid dependence during pregnancy. Effects and management. Obstet Gynecol Clin North Am 1998;25:139–51.

24. Finnegan LP. Treatment issues for opioid-dependent women during the perinatal period. J Psychoactive Drugs 1991;23: 191–201.

25. Zuspan FP, Gumpel JA, Mejia-Zelaya A, Madden J, Davis R. Fetal stress from methadone withdrawal. Am J Obstet Gynecol 1975;122:43–6.

26. Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2004.

27. Albright B, de la Torre L, Skipper B, Price S, Abbott P, Rayburn W. Changes in methadone maintenance therapy during and after pregnancy. J Subst Abuse Treat 2011;41:347–53.

28. Dashe JS, Sheffield JS, Olscher DA, Todd SJ, Jackson GL, Wendel GD. Relationship between maternal methadone dosage and neonatal withdrawal. Obstet Gynecol 2002;100:1244–9.

29. Berghella V, Lim PJ, Hill MK, Cherpes J, Chennat J, Kaltenbach K. Maternal methadone dose and neonatal withdrawal. Am J Obstet Gynecol 2003;189:312–7.

30. Cleary BJ, Eogan M, O'Connell MP, Fahey T, Gallagher PJ, Clarke T, et al. Methadone and perinatal outcomes: a prospective cohort study. Addiction 2012;107:1482–92.

31. Jones HE, Jansson LM, O'Grady KE, Kaltenbach K. The relationship between maternal methadone dose at delivery and neonatal outcome: methodological and design considerations. Neurotoxicol Teratol 2013;39:110–5.

32. Pizarro D, Habli M, Grier M, Bombrys A, Sibai B, Livingston J. Higher maternal doses of methadone does not increase neonatal abstinence syndrome. J Subst Abuse Treat 2011;40:295–8.

33. Cleary BJ, Donnelly J, Strawbridge J, Gallagher PJ, Fahey T, Clarke M, et al. Methadone dose and neonatal abstinence syndrome–systematic review and meta-analysis. Addiction 2010;105:2071–84.

34. Young JL, Martin PR. Treatment of opioid dependence in the setting of pregnancy. Psychiatr Clin North Am 2012;35: 441–60.

35. Mozurkewich EL, Rayburn WF. Buprenorphine and methadone for opioid addiction during pregnancy. Obstet Gynecol Clin North Am 2014;41:241–53.

36. Kraus ML, Alford DP, Kotz MM, Levounis P, Mandell TW, Meyer M, et al. Statement of the American Society of Addiction Medicine Consensus Panel on the use of buprenorphine in office-based treatment of opioid addiction. J Addict Med 2011;5:254–63.

37. Alto WA, O'Connor AB. Management of women treated with buprenorphine during pregnancy. Am J Obstet Gynecol 2011; 205:302–8.

38. Farid WO, Dunlop SA, Tait RJ, Hulse GK. The effects of maternally administered methadone, buprenorphine and naltrexone on offspring: review of human and animal data. Curr Neuropharmacol 2008;6:125–50.

39. Gryczynski J, Mitchell SG, Jaffe JH, Kelly SM, Myers CP, O'Grady KE, et al. Retention in methadone and buprenorphine treatment among African Americans. J Subst Abuse Treat 2013;45:287–92.

40. Bell JR, Butler B, Lawrance A, Batey R, Salmelainen P. Comparing overdose mortality associated with methadone and buprenorphine treatment. Drug Alcohol Depend 2009; 104:73–7.

41. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med 2010;363:2320–31.

42. Lester BM, Lagasse LL. Children of addicted women. J Addict Dis 2010;29:259–76.

43. Shiu JR, Ensom MH. Dosing and monitoring of methadone in pregnancy: literature review. Can J Hosp Pharm 2012;65:380–6.

44. Jansson LM, Dipietro JA, Velez M, Elko A, Knauer H, Kivlighan KT. Maternal methadone dosing schedule and fetal neurobehaviour. J Matern Fetal Neonatal Med 2009;22:29–35.

45. McCarthy JJ, Leamon MH, Willits NH, Salo R. The effect of methadone dose regimen on neonatal abstinence syndrome. J Addict Med 2015;9:105–10.

46. Jones HE, O'Grady KE, Malfi D, Tuten M. Methadone maintenance vs methadone taper during pregnancy: maternal and neonatal outcomes. Am J Addict 2008;17:372–86.

47. Holbrook AM, Jones HE, Heil SH, Martin PR, Stine SM, Fischer G, et al. Induction of pregnant women onto opioid-agonist maintenance medication: an analysis of withdrawal symptoms and study retention. Drug Alcohol Depend 2013; 132:329–34.

48. Holbrook AM, Baxter JK, Jones HE, Heil SH, Coyle MG, Martin PR, et al. Infections and obstetric outcomes in opioid-dependent pregnant women maintained on methadone or buprenorphine. Addiction 2012;107(suppl 1):83–90.

49. Gaalema DE, Scott TL, Heil SH, Coyle MG, Kaltenbach K, Badger GJ, et al. Differences in the profile of neonatal abstinence syndrome signs in methadone- versus buprenorphine-exposed neonates. Addiction 2012;107(suppl 1):53–62.

50. Gaalema DE, Heil SH, Badger GJ, Metayer JS, Johnston AM. Time to initiation of treatment for neonatal abstinence syndrome in neonates exposed in utero to buprenorphine or methadone. Drug Alcohol Depend 2013;133:266–9.

51. Brogly SB, Saia KA, Walley AY, Du HM, Sebastiani P. Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis. Am J Epidemiol 2014;180:673–86.

52. Johnson RE, Jones HE, Fischer G. Use of buprenorphine in pregnancy: patient management and effects on the neonate. Drug Alcohol Depend 2003;70(suppl):S87–101.

53. McNicholas LF, Holbrook AM, O'Grady KE, Jones HE, Coyle MG, Martin PR, et al. Effect of hepatitis C virus status on liver enzymes in opioid-dependent pregnant women maintained on opioid-agonist medication. Addiction 2012;107 (suppl 1):91–7.

54. Komaromy M, Buser R, Silver H, Hayes L, Bohan J, Duhigg D, et al. New Mexico treatment guidelines for medical providers who treat opioid addiction using buprenorphine. Santa Fe (NM): New Mexico Behavioral Health Collaborative; 2012.

55. Jones HE, Heil SH, Baewert A, Arria AM, Kaltenbach K, Martin PR, et al. Buprenorphine treatment of opioid-dependent pregnant women: a comprehensive review. Addiction 2012;107(suppl 1):5–27.

56. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. Clin Pharmacokinet 2005;44:661–80.

57. American Society of Addiction Medicine. National practice guideline for the use of medications in the treatment of addiction involving opioid use. Chevy Chase (MD): American Society of Addiction Medicine; 2015.

58. World Health Organization. Guidelines for identification and management of substance use and substance use disorders in

pregnancy. Geneva (Switzerland): World Health Organization; 2014.

59. Debelak K, Morrone WR, O'Grady KE, Jones HE. Buprenorphine + naloxone in the treatment of opioid dependence during pregnancy–initial patient care and outcome data. Am J Addict 2013;22:252–4.
60. Lund IO, Fischer G, Welle-Strand GK, O'Grady KE, Debelak K, Morrone WR, et al. A comparison of buprenorphine + naloxone to buprenorphine and methadone in the treatment of opioid dependence during pregnancy: maternal and neonatal outcomes. Subst Abuse 2013;7:61–74.
61. Wiegand SL, Stringer EM, Stuebe AM, Jones H, Seashore C, Thorp J. Buprenorphine and naloxone compared with methadone treatment in pregnancy. Obstet Gynecol 2015;125: 363–8.
62. Jumah NA, Edwards C, Balfour-Boehm J, Loewen K, Dooley J, Gerber Finn L, et al. Observational study of the safety of buprenorphine+naloxone in pregnancy in a rural and remote population. BMJ Open 2016;6:e011774.
63. Leslie DL, Milchak W, Gastfriend DR, Herschman PL, Bixler EO, Velott DL, et al. Effects of injectable extended-release naltrexone (XR-NTX) for opioid dependence on residential rehabilitation outcomes and early follow-up. Am J Addict 2015;24:265–70.
64. Cousins SJ, Radfar SR, Crevecoeur-MacPhail D, Ang A, Darfler K, Rawson RA. Predictors of continued use of extended-released naltrexone (XR-NTX) for opioid-dependence: an analysis of heroin and non-heroin opioid users in Los Angeles County. J Subst Abuse Treat 2016;63:66–71.
65. Lee JD, Friedmann PD, Kinlock TW, Nunes EV, Boney TY, Hoskinson RA Jr, et al. Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. N Engl J Med 2016;374:1232–42.
66. Saia KA, Schiff D, Wachman EM, Mehta P, Vilkins A, Sia M, et al. Caring for pregnant women with opioid use disorder in the USA: expanding and improving treatment. Curr Obstet Gynecol Rep 2016;5:257–263.
67. Jones HE, Chisolm MS, Jansson LM, Terplan M. Naltrexone in the treatment of opioid-dependent pregnant women: the case for a considered and measured approach to research. Addiction 2013;108:233–47.
68. Dashe JS, Jackson GL, Olscher DA, Zane EH, Wendel GD Jr. Opioid detoxification in pregnancy. Obstet Gynecol 1998;92: 854–8.
69. Luty J, Nikolaou V, Bearn J. Is opiate detoxification unsafe in pregnancy? J Subst Abuse Treat 2003;24:363–7.
70. Stewart RD, Nelson DB, Adhikari EH, McIntire DD, Roberts SW, Dashe JS, et al. The obstetrical and neonatal impact of maternal opioid detoxification in pregnancy. Am J Obstet Gynecol 2013;209:267.e1–5.
71. Lund IO, Fitzsimons H, Tuten M, Chisolm MS, O'Grady KE, Jones HE. Comparing methadone and buprenorphine maintenance with methadone-assisted withdrawal for the treatment of opioid dependence during pregnancy: maternal and neonatal outcomes. Subst Abuse Rehabil 2012;3(suppl 1):17–25.
72. Bell J, Towers CV, Hennessy MD, Heitzman C, Smith B, Chattin K. Detoxification from opiate drugs during pregnancy. Am J Obstet Gynecol 2016;215:374.e1–6.
73. Blinick G, Wallach RC, Jerez E, Ackerman BD. Drug addiction in pregnancy and the neonate. Am J Obstet Gynecol 1976;125:135–42.
74. Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011;204:314.e1–11.
75. Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. Obstet Gynecol 2013;122:838–44.
76. Zedler BK, Mann AL, Kim MM, Amick HR, Joyce AR, Murrelle EL, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. Addiction 2016;111:2115–28.
77. Parikh R, Hussain T, Holder G, Bhoyar A, Ewer AK. Maternal methadone therapy increases QTc interval in newborn infants. Arch Dis Child Fetal Neonatal Ed 2011;96:F141–3.
78. Archie CL, Lee MI, Sokol RJ, Norman G. The effects of methadone treatment on the reactivity of the nonstress test. Obstet Gynecol 1989;74:254–5.
79. Levine AB, Rebarber A. Methadone maintenance treatment and the nonstress test. J Perinatol 1995;15:229–31.
80. Anyaegbunam A, Tran T, Jadali D, Randolph G, Mikhail MS. Assessment of fetal well-being in methadone-maintained pregnancies: abnormal nonstress tests. Gynecol Obstet Invest 1997;43:25–8.
81. Benningfield MM, Arria AM, Kaltenbach K, Heil SH, Stine SM, Coyle MG, et al. Co-occurring psychiatric symptoms are associated with increased psychological, social, and medical impairment in opioid dependent pregnant women. Am J Addict 2010; 19:416–21.
82. Ouimette PC, Kimerling R, Shaw J, Moos RH. Physical and sexual abuse among women and men with substance use disorders. Alcohol Treat Q 2008;18:7–17.
83. Terplan M, McNamara EJ, Chisolm MS. Pregnant and nonpregnant women with substance use disorders: the gap between treatment need and receipt. J Addict Dis 2012;31:342–9.
84. Terplan M, Longinaker N, Appel L. Women-centered drug treatment services and need in the United States, 2002–2009. Am J Public Health 2015;105:e50–4.
85. Jones HE, Deppen K, Hudak ML, Leffert L, McClelland C, Sahin L, et al. Clinical care for opioid-using pregnant and postpartum women: the role of obstetric providers. Am J Obstet Gynecol 2014;210:302–10.
86. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med 2006;144:127–34.
87. Meyer M, Wagner K, Benvenuto A, Plante D, Howard D. Intrapartum and postpartum analgesia for women maintained on methadone during pregnancy. Obstet Gynecol 2007;110: 261–6.
88. Meyer M, Paranya G, Keefer Norris A, Howard D. Intrapartum and postpartum analgesia for women maintained on buprenorphine during pregnancy. Eur J Pain 2010;14:939–43.
89. Winklbaur B, Kopf N, Ebner N, Jung E, Thau K, Fischer G. Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence: a knowledge synthesis for better treatment for women and neonates. Addiction 2008;103:1429–40.
90. Substance Abuse and Mental Health Services Administration. Medication-assisted treatment for opioid addiction in opioid treatment programs. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2005.
91. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain–United States, 2016. MMWR Recomm Rep 2016;65:1–49.

92. Kantor TG, Cantor R, Tom E. A study of hospitalized surgical patients on methadone maintenance. Drug Alcohol Depend 1980;6:163–73.

93. Wightman R, Perrone J, Portelli I, Nelson L. Likeability and abuse liability of commonly prescribed opioids. J Med Toxicol 2012;8:335–40.

94. Bateman BT, Huybrechts KF, Booth J, Briggs H, Flood P, Bauer M, et al. Opioid use following discharge after cesarean delivery. Pharmacoepidemiol Drug Saf 2016;25:567.

95. Bateman BT, Franklin JM, Bykov K, Avorn J, Shrank WH, Brennan TA, et al. Persistent opioid use following cesarean delivery: patterns and predictors among opioid-naive women. Am J Obstet Gynecol 2016;215:353.e1–18.

96. Gopman S. Prenatal and postpartum care of women with substance use disorders. Obstet Gynecol Clin North Am 2014;41: 213–28.

97. Jansson LM, Velez M, Harrow C. Methadone maintenance and lactation: a review of the literature and current management guidelines. J Hum Lact 2004;20:62–71.

98. Demirci JR, Bogen DL, Klionsky Y. Breastfeeding and methadone therapy: the maternal experience. Subst Abus 2015;36: 203–8.

99. Abdel-Latif ME, Pinner J, Clews S, Cooke F, Lui K, Oei J. Effects of breast milk on the severity and outcome of neonatal abstinence syndrome among infants of drug-dependent mothers. Pediatrics 2006;117:e1163–9.

100. Jansson LM, Choo R, Velez ML, Harrow C, Schroeder JR, Shakleya DM, et al. Methadone maintenance and breastfeeding in the neonatal period. Pediatrics 2008;121:106–14.

101. Dryden C, Young D, Hepburn M, Mactier H. Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. BJOG 2009;116:665–71.

102. McQueen KA, Murphy-Oikonen J, Gerlach K, Montelpare W. The impact of infant feeding method on neonatal abstinence scores of methadone-exposed infants. Adv Neonatal Care 2011;11:282–90.

103. Pritham UA, Paul JA, Hayes MJ. Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. J Obstet Gynecol Neonatal Nurs 2012;41:180–90.

104. Welle-Strand GK, Skurtveit S, Jansson LM, Bakstad B, Bjarkø L, Ravndal E. Breastfeeding reduces the need for withdrawal treatment in opioid-exposed infants. Acta Paediatr 2013; 102:1060–6.

105. Lindemalm S, Nydert P, Svensson JO, Stahle L, Sarman I. Transfer of buprenorphine into breast milk and calculation of infant drug dose. J Hum Lact 2009;25:199–205.

106. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics 2001;108:776–89.

107. Ballard JL. Treatment of neonatal abstinence syndrome with breast milk containing methadone. J Perinatal Neonatal Nurs 2002;15:76–85.

108. McCarthy JJ, Leamon MH, Parr MS, Anania B. High-dose methadone maintenance in pregnancy: maternal and neonatal outcomes. Am J Obstet Gynecol 2005;193:606–10.

109. Wachman EM, Byun J, Philipp BL. Breastfeeding rates among mothers of infants with neonatal abstinence syndrome. Breastfeed Med 2010;5:159–64.

110. O'Connor AB, Collett A, Alto WA, O'Brien LM. Breastfeeding rates and the relationship between breastfeeding and neonatal abstinence syndrome in women maintained on buprenorphine during pregnancy. J Midwifery Womens Health 2013;58:383–8.

111. Academy of Breastfeeding Medicine Protocol Committee, Jansson LM. ABM clinical protocol #21: Guidelines for breastfeeding and the drug-dependent woman. Breastfeed Med 2009;4:225–8.

112. Jansson LM, Spencer N, McConnell K, Velez M, Tuten M, Harrow CA, et al. Maternal buprenorphine maintenance and lactation. J Hum Lact 2016;32:675–681.

113. Heil SH, Jones HE, Arria A, Kaltenbach K, Coyle M, Fischer G, et al. Unintended pregnancy in opioid-abusing women. J Subst Abuse Treat 2011;40:199–202.

114. Black KI, Stephens C, Haber PS, Lintzeris N. Unplanned pregnancy and contraceptive use in women attending drug treatment services. Aust N Z J Obstet Gynaecol 2012;52: 146–50.

115. Armstrong KA, Kennedy MG, Kline A, Tunstall C. Reproductive health needs: comparing women at high, drug-related risk of HIV with a national sample. J Am Med Womens Assoc (1972) 1999;54:65–70, 78.

116. Terplan M, Lawental M, Connah MB, Martin CE. Reproductive health needs among substance use disorder treatment clients. J Addict Med 2016;10:20–5.

117. Armstrong KA, Kenen R, Samost L. Barriers to family planning services among patients in drug treatment programs. Fam Plann Perspect 1991;23:264–6, 270–1.

118. Ralph N, Spigner C. Contraceptive practices among female heroin addicts. Am J Public Health 1986;76:1016–7.

119. Morrison CL, Ruben SM, Beeching NJ. Female sexual health problems in a drug dependency unit. Int J STD AIDS 1995;6: 201–3.

120. Terplan M, Hand DJ, Hutchinson M, Salisbury-Afshar E, Heil SH. Contraceptive use and method choice among women with opioid and other substance use disorders: a systematic review. Prev Med 2015;80:23–31.

121. Sinha C, Guthrie KA, Lindow SW. A survey of postnatal contraception in opiate-using women. J Fam Plann Reprod Health Care 2007;33:31–4.

122. Tocce KM, Sheeder JL, Teal SB. Rapid repeat pregnancy in adolescents: do immediate postpartum contraceptive implants make a difference? Am J Obstet Gynecol 2012;206:481.e1–7.

123. Ogburn JA, Espey E, Stonehocker J. Barriers to intrauterine device insertion in postpartum women. Contraception 2005; 72:426–9.

124. Parlier AB, Fagan B, Ramage M, Galvin S. Prenatal care, pregnancy outcomes, and postpartum birth control plans among pregnant women with opiate addictions. South Med J 2014;107:676–83.

125. Fitzsimons HE, Tuten M, Vaidya V, Jones HE. Mood disorders affect drug treatment success of drug-dependent pregnant women. J Subst Abuse Treat 2007;32:19–25.

126. Benningfield MM, Dietrich MS, Jones HE, Kaltenbach K, Heil SH, Stine SM, et al. Opioid dependence during pregnancy: relationships of anxiety and depression symptoms to treatment outcomes. Addiction 2012;107(suppl 1):74–82.

127. Chapman SL, Wu LT. Postpartum substance use and depressive symptoms: a review. Women Health 2013;53:479–503.

128. Finnegan LP, Connaughton JF Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. Addict Dis 1975;2:141–58.

129. Lipsitz PJ, Blatman S. Newborn infants of mothers on methadone maintenance. N Y State J Med 1974;74:994–9.

130. Jansson LM, Velez ML. Infants of drug-dependent mothers. Pediatr Rev 2011;32:5–12.

131. Hudak ML, Tan RC; Committee on Drugs; Committee on the Fetus and Newborn; American Academy of Pediatrics. Neonatal drug withdrawal. Pediatrics 2012;129:e540–60.

132. Ostrea EM Jr, Chavez CJ, Strauss ME. A study of factors that influence the severity of neonatal narcotic withdrawal. Addict Dis 1975;2:187–99.

133. Green M, Suffet F. The Neonatal Narcotic Withdrawal Index: a device for the improvement of care in the abstinence syndrome. Am J Drug Alcohol Abuse 1981;8:203–13.

134. Zahorodny W, Rom C, Whitney W, Giddens S, Samuel M, Maichuk G, et al. The neonatal withdrawal inventory: a simplified score of newborn withdrawal. J Dev Behav Pediatr 1998;19:89–93.

135. Jansson LM, Velez M, Harrow C. The opioid-exposed newborn: assessment and pharmacologic management. J Opioid Manag 2009;5:47–55.

136. Wachman EM, Newby PK, Vreeland J, Byun J, Bonganzi A, Bauchner H, et al. The relationship between maternal opioid agonists and psychiatric medications on length of hospitalization for neonatal abstinence syndrome. J Addict Med 2011;5:293–9.

137. Wachman EM, Hayes MJ, Brown MS, Paul J, Harvey-Wilkes K, Terrin N, et al. Association of OPRM1 and COMT single-nucleotide polymorphisms with hospital length of stay and treatment of neonatal abstinence syndrome. JAMA 2013;309:1821–7.

138. Wachman EM, Hayes MJ, Lester BM, Terrin N, Brown MS, Nielsen DA, et al. Epigenetic variation in the mu-opioid receptor gene in infants with neonatal abstinence syndrome. J Pediatr 2014;165:472–8.

139. Patrick SW, Schumacher RE, Horbar JD, Buus-Frank ME, Edwards EM, Morrow KA, et al. Improving care for neonatal abstinence syndrome. Pediatrics 2016 [Epub ahead of print].

140. Velez M, Jansson LM. The Opioid dependent mother and newborn dyad: non-pharmacologic care. J Addict Med 2008; 2:113–20.

141. Tolia VN, Patrick SW, Bennett MM, Murthy K, Sousa J, Smith PB, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. N Engl J Med 2015;372:2118–26.

142. Asti L, Magers JS, Keels E, Wispe J, McClead RE Jr. A quality improvement project to reduce length of stay for neonatal abstinence syndrome. Pediatrics 2015;135:e1494–500.

143. Baldacchino A, Arbuckle K, Petrie DJ, McCowan C. Neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis [published erratum appears in BMC Psychiatry 2015;15:134]. BMC Psychiatry 2014;14:104.