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Opioid use disorder in pregnancy

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Abstract

The number of pregnant people affected by the opioid epidemic in the United States continues to rise. The following key aspects of opioid use disorder in pregnancy are explored through the progression of a pregnancy via a patient case: treatment options, treatment decisions, substance use screening, dosing modifications, and other aspects of peripartum care. Many factors affect opioid use disorder treatment choices during pregnancy; however, when a pregnant person is medically eligible for a therapy and multiple options are available locally, the ultimate decision regarding treatment selection should be left up to the patient and strong support services provided. This approach to treatment results in optimal maternal and neonatal outcomes and long-term maternal engagement and retention in care.

Keywords: opioid use disorder (OUD), medication-assisted treatment (MAT), buprenorphine, methadone, neonatal abstinence syndrome (NAS), neonatal opioid withdrawal syndrome (NOWS), breastfeeding, labor and delivery pain, precipitated withdrawal

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Introduction

According to the Centers for Disease Control, the prevalence of opioid use disorder (OUD) during pregnancy more than quadrupled from 1999 to 2014.[1] From 2002 to 2009, neonatal abstinence syndrome (NAS) from maternal opioid use increased 5-fold, resulting in 1 baby born with NAS every 30 minutes,[2] further increasing to 1 every 15 minutes by January 2018.[3]

In addition to NAS, OUD during pregnancy can result in significant negative maternal and neonatal medical and social consequences.[4-6] Pregnancy-specific examples include preterm labor, fetal convulsions, intrauterine fetal demise, and intrauterine meconium passage.[4,6-10] Fetal distress and withdrawal also result from repeated daily cycles of maternal opioid use and withdrawal. These cycles negatively impact placental function and can cause intrauterine growth restriction, placental abruption, preterm delivery, and low birth weight.[4,6,10] Also, limited data indicates a low absolute risk but increased relative risk of birth defects from prescription opioid use during pregnancy, including heart defects, spina bifida, and gastroschisis.[6,8,11] Fortunately, many women affected by OUD are motivated to stop or reduce illicit opioid use during pregnancy and engage in prenatal care for the best outcome for their child(ren) and to prevent the removal of their child(ren) via Child Protective Services (CPS).[2] Data indicate pregnant people with OUD are more likely to initiate treatment and remain abstinent when permitted to stay with their child(ren).[12] Therefore, pregnancy

presents a significant window of opportunity for treating and effectively managing OUD. This article will review OUD in pregnancy via a case discussion.

Case

Lilly, a 30-year-old G2P0010 pregnant person at 12 weeks 3 days gestation, presents to an obstetric and gynecology clinic for a first prenatal visit after having a positive home pregnancy test 3 days ago. The patient prefers the pronouns she, her, and hers. Per patient report, this pregnancy is desired. Lilly works full time as a fashion designer and attends night classes towards a business degree. Her partner is a computer programmer for a local startup company. Lilly has a past medical history significant for generalized anxiety disorder. She has no known drug allergies, and current medications are one prenatal vitamin and sertraline 100 mg taken by mouth daily. A physical examination reveals normal vital signs, weight of 65 kg, height of 5 ft 6 in (1.68 m), and a confirmed intrauterine pregnancy on ultrasound. The patient appears concerned and reveals she self-medicates with illegally purchased oxycodone to cope with the trauma of a friend who died by suicide last year. She endorses illicit use for over a year, difficulty stopping illicit use, and desires to start treatment because she "doesn't want her baby taken away." Lilly wants to know what the treatment options are and if any of these options will "hurt her baby." She did a web search for oxycodone and read it has a pregnancy category C designation but said she does not know what that means.

General Principles of OUD in Pregnancy

Before discussing Lilly's options, one must understand basic pregnancy terminology, know how to access relevant literature, and be able to correctly analyze drug information with regard to different pregnancy stages. See the Box for general information and resources in pregnancy and lactation. Lilly's pregnancy is desired, and a goal for her pregnancy is a live delivery at term, preferably between 39 and 41 weeks. Lilly's illicit opioid use disclosure is an excellent window of opportunity to engage her in OUD treatment and prevent a preterm birth along with other untreated OUD risks. Lilly's confusion about the pregnancy category C designation for oxycodone has been common among patients and providers for decades. Pharmacists and other providers must rely on current scientific data instead of pregnancy categories when practicing shared clinical decision-making.

Treatment Options and Decisions

There are several OUD treatment options for pregnant patients. The standard of care is medication-assisted treatment (MAT) with either buprenorphine or methadone as these options result in improved maternal and neonatal outcomes.[4,8] Both medications are Food and Drug Administration (FDA) approved for OUD treatment in pregnancy and are recommended as first line options by leading experts in widely recognized organizations devoted to improving maternal and child health,[2,8,12] including the American College of Obstetricians and Gynecologists (ACOG), the Substance Abuse and Mental Health Services Administration (SAMHSA), and the World Health Organization (WHO). It is important to note that both treatments have the best outcomes when combined with robust psychosocial therapy and support through counseling, comorbid condition treatment, case management, parental support and education, and employment training.[21] Ideally, pregnancy-specific programs should incorporate pharmacologic treatment, but most states do not have these programs.[2] However, accessing available resources such as safe housing, reliable transportation, child care, prenatal care, and vocational assistance are important in devising a treatment plan because these resources can affect a pregnant person's likelihood of entering and remaining in care. For example, there is evidence that treatment retention rates increase when mothers living with children are able to bring their children to treatment appointments.[5]

Other treatment options for OUD in pregnancy include naltrexone and medically assisted withdrawal (MAW); however, neither is first line, and maternal and neonatal risks are not fully understood. Naltrexone has limited data for use in pregnancy, but if a pregnant patient declines first line agents and prefers naltrexone, it is not absolutely contraindicated.[21,22] Risks and the limitations of current

Take Home Points

1. Maintenance medication-assisted treatment during pregnancy with either buprenorphine or methadone works.
2. The decision to use buprenorphine or methadone should be patient-centered.
3. Medication dosing and frequency adjustments due to the dynamic physiological changes during and after pregnancy should be made based on maternal symptoms and cravings.
4. Breastfeeding is safe with maternal medication-assisted treatment and reduces neonatal abstinence syndrome.
5. The home buprenorphine or methadone regimen should be continued during labor, delivery, and postpartum.

BOX: General information and resources for pregnancy and breastfeeding

Terminology:	
Gravida (G) #	Refers to the number of times a patient has been pregnant
Para (P) #	Refers to the number of times a patient has delivered
Example: G4P1021	Patient has been pregnant 4 times (including the current pregnancy) and has had 1 term infant, no preterm infants, 2 abortions, and has 1 living child
Term pregnancy	A pregnancy that reaches 37 weeks gestation
Late preterm neonate	A neonate born between 37 and 39 weeks
Previable	A fetus highly unlikely to survive after birth during the first or second trimester. Many states in the United States have different time cut off limits for previability; but, generally, a fetus under 24 weeks gestation is considered previable.
Pregnancy Categories:	Pregnancy categories (A, B, C, D, X) were removed from all new FDA labeling on June 30, 2015 via the FDA Pregnancy and Lactation Labeling Rule and were replaced with a synopsis of relevant data regarding pregnancy, lactation, and female and male reproductive potential. These categories were notoriously interpreted incorrectly and resulted in treatment decisions that did not necessarily take into account the underlying information used to determine the category designation. Unfortunately, some drug information resources still list the old category designations.
Resources:	
Reprotox	https://reprotox.org/
Lactmed	https://toxnet.nlm.nih.gov/
Infant Risk Center	https://www.infantrisk.com/
ACOG	https://www.acog.org/
HIVE	https://hiveonline.org/
Physiology of Pregnancy:	
Pharmacokinetic changes	Decreased gastrointestinal motility, increased gastric pH and blood flow, increased total body water and plasma volume resulting in a larger volume of distribution, decreased drug binding concentrations, increased glomerular filtration rate, and increased number of drug-metabolizing enzymes in the liver such as CYP3A4, CYP2D6, and CYP2C9.[13,14]
Labor and Delivery Basics:	
Mode of delivery	Vaginal delivery is expected unless there is a contraindication. Some pregnant people labor for several days and then need a cesarean section with subsequent recovery and a longer hospital stay.
Pain management	Multi-modal pain management with options that reduce peripartum opioid use should be used for all patients. Options during labor and delivery may include: • Nonpharmacologic measures, such as massage, doula support, and position changes • Use of neuraxial, regional, and local anesthesia • Early epidural placement • Inhaled nitrous oxide • Neuraxial long-acting opioid administration • Multi-modal pain control options, including NSAIDs and acetaminophen, during the postpartum period • Epidural analgesia maintained for the first 24 hours post-delivery • IV acetaminophen (may be preferred compared to the oral formulation)[15] • Preoperative administration of gabapentin and/or acetaminophen (shown to reduce post-operative pain in non-obstetrical surgical procedures and can be used for cesarean sections)[15] • Nonopioid adjunctive medications, such as ketamine and dexmedetomidine, for severe pain (data limited) • Epidural magnesium sulfate (limited data show reduced pain and opioid requirements during and after cesarean delivery)[16]
Breastfeeding:	
Neonatal benefits	Lower risk of childhood diseases such as asthma, leukemia, obesity, ear infections, eczema, diarrhea, vomiting, lower respiratory tract infections, necrotizing enterocholitis (NEC), sudden infant death syndrome (SIDS), and Type II diabetes[17]
Maternal benefits	Decreased risk for certain breast cancers, ovarian cancer, postpartum depression, and Type II diabetes;[4] faster recovery from childbirth, including faster weight loss; reduction in cost;[18] decrease in maternal stress, which promotes better mother-child bonding;[19] reduction in maternal neglect and child abuse rates[20]

data, however, still need to be discussed with the patient. Animal studies with naltrexone have demonstrated higher rates of large-for-gestational-age offspring, but limited available data for human birth outcomes have been normal.[23-26] Although not specifically studied in the peripartum period, patients should additionally be made aware that if naltrexone is the selected treatment option, opioids are unlikely to be effective for pain control during labor, delivery, and postpartum. Medically assisted withdrawal is also not recommended because it is associated with high recidivism rates (59%-90%) and fetal intolerance,[8,27] and there are limited data on maternal and neonatal outcomes post-delivery.[28] However, MAW is also not absolutely contraindicated. Some experts believe and there is some evidence MAW can be safely performed during pregnancy under the care of a provider trained in perinatal addiction medicine after informed consent. Experts believe, however, that successful MAW may necessitate an inpatient hospital stay and intense outpatient follow-up.[22]

The question remains, how does one make the decision between buprenorphine and methadone when a patient is interested in a first-line option? When a pregnant person is medically eligible for either first-line option and both are available locally, patient preference is the deciding factor. Identifying what factors are most important to a patient and using a shared decision-making model allows for optimal outcomes as this model has been shown to improve adherence and treatment retention in other areas of medicine.[29] The factors often most important to a pregnant patient affected by OUD are summarized in Table 1 and detailed below. Highlighting the differences between the two treatments aids pregnant people in making the best decision for themselves.

Efficacy

The treatment goals for both buprenorphine and methadone are the same: cessation of illicit opioid use, opioid withdrawal symptoms, and cravings; positive neonatal outcomes; and sustained maternal engagement and retention in care. Buprenorphine and methadone have both been proven to be highly effective for OUD treatment during pregnancy, reduce risks to mother and baby from untreated OUD, prevent maternal relapse, prevent separation of families via CPS involvement, and aid parents in providing an environment for optimal childhood growth and development.[21] Methadone has been used to successfully treat pregnant people with OUD since the 1970s and became the standard of care in the United States by 1998.[8,42] Methadone has been shown to reduce illicit opioid use and maternal mortality and increase engagement in prenatal care.[33] Buprenorphine treatment for OUD in pregnancy is a more recent development with increased use over the last several years[43] and it has proven to reduce illicit opioid use, injection drug use, overdose deaths, and overall mortality.[32]

Treatment with these medications has also been shown to result in positive neonatal outcomes, including increases in neonatal birth weight, gestational age at delivery, and head circumference.[8,33,35,36] Ideally, a pregnant person affected by OUD should start treatment with either buprenorphine or methadone upon initial presentation to care in order to obtain the best outcomes as evidence has demonstrated that pregnant people are more likely to remain abstinent the longer they are abstinent during pregnancy.[44] There are risks associated with both treatments as discussed subsequently; however, these risks are considered minimal compared to the risks of untreated OUD.[2]

Treatment Retention

Key differences between the two medications are the treatment initiation process and retention. There is no consensus on optimal MAT dosing protocols in pregnancy. Induction protocols for nonpregnant individuals can be used for those who are pregnant, but buprenorphine's partial mu-opioid receptor agonist and alpha-kappa opioid receptor antagonist activity can precipitate withdrawal.[43] Therefore, buprenorphine induction with the sublingual (SL) form requires a pregnant person to be in some withdrawal before taking a first dose,[43] while methadone does not. This withdrawal is unpleasant, is not always tolerated, and may be a barrier to care. In a landmark study known as the MOTHER (Maternal Opioid Treatment: Human Experimental Research) trial, which is the largest randomized controlled trial to date comparing buprenorphine to methadone for OUD treatment in 175 pregnant people, there was a statistically significant increase in dropout rates for those taking SL buprenorphine for OUD in pregnancy (33%) compared to those taking methadone (18%). Most dropouts occurred during induction, but retention rates were similar between groups after inductions were completed.[34] It is hypothesized that the higher drop out rates during induction in the MOTHER trial may have been due to patients experiencing precipitated withdrawal. Data available from nonpregnancy settings show people maintained on buprenorphine at doses above 16 mg have the same retention rates as people in methadone treatment,[45] further indicating the true impact of medication choice on retention is unclear, but it is important to acknowledge the possibility of lower retention rates with buprenorphine compared to methadone. Some new data in nonpregnant people suggest the use of the buprenorphine patch formulation for buprenorphine inductions may prevent precipitated withdrawal and may allow patients to avoid

TABLE 1: Key differences between MAT options for OUD treatment in pregnancy

Key Factors	Buprenorphine[a]	Methadone
Efficacy	Results in abstinence from illicit opioid use Reduces opioid use, injection drug use, overdose deaths, and overall mortality[32]	Results in abstinence from illicit opioid use Reduces opioid use, injection drug use, overdose deaths, and overall mortality[33]
Treatment retention	Higher dropout rates initially compared to methadone[34]	Lower dropout rates overall compared to buprenorphine[34]
Maternal withdrawal	Mild withdrawal often required before initiation	Withdrawal not required for initiation
Neonatal outcomes	Lower rates of preterm birth, low birth weights, and smaller head circumferences compared to no treatment[8,35,36] Higher average gestational age at birth, head circumference, length at birth, and average birth weight compared to methadone[34] Less long-term neurodevelopment outcome data than methadone	Lower rates of preterm birth, low birth weights, and smaller head circumferences compared to no treatment[8,33,35,36]
NAS[b]	Present, but less severe compared to methadone MOTHER trial[34]: • Average length of hospital stay = 10 d • Average amount of morphine for treatment = 1.1 mg	Present, but more severe compared to buprenorphine MOTHER trial[34]: • Average length of hospital stay = 17.5 d • Average amount of morphine for treatment = 10.4 mg
Maternal clinic visits	Frequency: Initially, daily or weekly visits, which are then spaced out to biweekly or monthly Location: medical clinic (eg, prenatal, primary care, psychiatric, or addiction clinic) or OTP	Frequency: Daily for at least the first 3 months, which can then be spaced out with take-home doses Location: OTP (ie, methadone clinic)
Maternal side effects	Less sedating compared to methadone Lower risk of cardiovascular side effects compared to methadone Nausea and constipation, but mild and self-limiting	More dose-dependent sedation compared to buprenorphine and higher risk for respiratory depression Small increased risk of arrhythmia
Pain management during labor and delivery	Home MAT regimen is not generally adequate for pain control but may be continued during labor and delivery Providers may offer both additional opioids and non-opioid analgesics	Home MAT regimen is not generally adequate for pain control but may be continued during labor and delivery Providers may offer both additional opioids and non-opioid analgesics
Breastfeeding	Recommended Reduces NAS Mothers have better bonding and improved recovery from birth[23,38] Transfer to breast milk is low,[39] equaling fewer morphine milligram equivalents than what a neonate would receive for NAS[40] If buprenorphine/naloxone product, naloxone is unlikely to negatively impact the child[41]	Recommended Reduces NAS Mothers have better bonding and improved recovery from birth[23,38] Transfer to breast milk is low,[39] equaling fewer morphine milligram equivalents than what a neonate would receive for NAS[40]

MAT = medication-assisted treatment, NAS = Neonatal Abstinence Syndrome, OUD = opioid use disorder, OTP = opioid treatment program.

[a]Some pregnant people established on MAT with methadone prior to pregnancy wish to switch to buprenorphine treatment. Although possible, there are no compelling reasons to switch, and it is difficult to do,[30] risks patient destabilization and relapse,[31] and is not recommended by the American College of Obstetricians and Gynecologists.[22]

[b]A condition with symptoms that may include high-pitched crying, abnormal sleeping patterns, increased muscle tone, tremors, convulsions, yawning, sweating, sneezing, poor feeding, excessive sucking, vomiting, diarrhea, increased respiratory rate, low grade fever, and irritability. Very severe forms of NAS can result in seizures, failure to thrive, and death.[4,37]

going through withdrawal all together during an induction.[46,47] This has not been studied in those who are pregnant with OUD, but the patch may eventually prove useful in reducing dropout rates for buprenorphine inductions in this population.

Neonatal Outcomes

For optimal fetal development and neonatal outcomes, ideally, a pregnant patient should avoid taking unnecessary medications; however, both buprenorphine and methadone are considered necessary for OUD treatment. Both options cross the placenta and fetal blood brain barrier, resulting in fetal exposure, but they do so at a steady state rather than via repeated daily cycles of large illicit opioid exposures followed by withdrawal. Low steady state levels from maternal OUD treatment with buprenorphine or methadone used to eliminate cravings, withdrawal, and relapse also minimize overall opioid exposure.[21]

Methadone is found in cord blood, amniotic fluid, and newborn urine.[48] Fetal risks of methadone from mothers with or without OUD compared to no fetal methadone exposure in the same population include a decrease in fetal growth and birth weight, reduced fetal length, smaller head circumference, a possible decrease in childhood psychometric and behavioral test scores, and a relative risk but very low absolute risk of teratogenicity.[2,49] However, metrics for preterm birth rates, birth weight, and head circumference are improved compared to untreated OUD as stated in Table 1.[2] Buprenorphine and its active metabolite cross the placenta to a lesser extent than methadone, which reduces overall opioid exposure to the fetus even more than methadone.[50,51] However, buprenorphine is still found in neonatal meconium, blood, and urine.[52] According to a systematic review[53] that included low quality studies with confounding variables, fetal risks from maternal buprenorphine treatment may include an association with oral clefts, cardiac defects, and club foot. There is also conflicting evidence on whether buprenorphine treatment results in lower birth weight and head circumference compared to nonopioid-dependent pregnant patients,[4] and there are limited data regarding long-term child developmental and behavioral outcomes.

Should a pregnant person choose buprenorphine for OUD treatment, use of the SL buprenorphine-only tablet is recommended over combination products with naloxone to date. Naloxone crosses the placenta[54] and is thought to potentially cause fetal withdrawal.[4] Endogenous opioids mediate various neurologic functions, and it is not fully understood what the consequences are of blocking these mediators.[55] The long-term effects of naloxone are also unknown, but there have been no reported negative neonatal outcomes with the combination products, and some evidence indicates they are safe to use in pregnancy.[56,57] As such, the buprenorphine naloxone combination products are considered acceptable alternatives if the patient prefers them or if availability of the buprenorphine-only product is limited.[2] Naloxone, however, is still the treatment of choice for overdose in pregnancy.[22] Additionally, if a patient was taking buprenorphine with naloxone before pregnancy, it is reasonable to switch to buprenorphine monotherapy in a one-to-one conversion and then switch the patient back to the combination product after delivery.

When compared to each other, buprenorphine and methadone have been shown to have several neonatal outcome differences. In the MOTHER trial, the authors[34] found statistically significant neonatal benefits of buprenorphine over methadone, including an increase in birth weight and head circumference along with reductions in preterm birth rates and lengths of hospital stay. Additionally, a secondary analysis demonstrated statistically significant increases in fetal heart rate variability and accelerations, movement, and movement duration in mothers who were exposed to buprenorphine compared to methadone. Although unknown whether clinically significant, these characteristics of fetal physiology are indicative of positive fetal health.[58] Other studies have also demonstrated an increase in fetal activity and heart rate variability,[59] higher average gestational ages at birth, and higher average birth weights with buprenorphine treatment compared to methadone.[60,61]

Neonatal Abstinence Syndrome

Risk for NAS, also known as neonatal opioid withdrawal syndrome (NOWS), is a neonatal outcome that often impacts the maternal decision of OUD treatment in pregnancy. Long-term effects are unclear, but this syndrome is a constellation of opioid withdrawal symptoms affecting the neonatal central nervous, autonomic nervous, and gastrointestinal systems and results from in-utero fetal opioid exposure immediately followed by abrupt withdrawal at delivery. This syndrome is associated with both untreated and treated OUD,[62] and 50% to 70% of affected neonates require pharmacologic treatment.[37,63] Neonatal abstinence syndrome can occur shortly after delivery, but may take up to 5 to 7 days to appear. It usually presents faster from maternal buprenorphine treatment and although rare, can occur up to a month after delivery in those infants exposed to methadone treatment in utero.[64] This variability in presentation has led the American Academy of Pediatrics to recommend 5 to 7 days of in-hospital monitoring of neonates born to mothers with OUD because NAS requires hospitalization, often in a NICU, with nonpharmacologic and pharmacologic treatment.[2]

In the MOTHER trial,[34] there was no statistically significant difference in the number of neonates needing treatment for NAS between buprenorphine and methadone, but there were statistically significant reductions in NAS duration, amount of morphine required for NAS treatment, and length of hospital stay with maternal buprenorphine treatment. See Table 1. The reasoning is thought to be multifactorial and includes buprenorphine's lower bioavailability, less placental transfer, and less intrinsic mu-opioid receptor activity compared to methadone.[34,59]

Regardless of whether a reduction in the effects of NAS is of high importance to a pregnant person, every patient should be counseled that newborns are not born *addicted* to opioids. Instead, in-utero physiologic dependence can result in subsequent withdrawal.[65] Additionally, they should be counseled that the risk and severity of NAS do not correlate with the chosen MAT dose,[23,37,66,67] and NAS from MAT is less severe than in the absence of treatment.[41] Furthermore, reducing medication doses in order to limit fetal exposure has been linked to an increase in illicit drug use and its subsequent risks.[7] Dosing decisions should only focus on maternal opioid cravings to prevent relapse.[68] New mothers can, however, reduce NAS severity through rooming in with their neonate, providing skin-to-skin contact, breastfeeding, minimizing environmental stimuli, and comforting the baby via swaying, rocking, and providing a pacifier.[37,69]

Maternal Impact

Maternal risks of methadone treatment include overdose, hypotension, bradycardia, cardiac arrhythmia, respiratory depression, and QTc prolongation.[70] The latter can be concerning because of risk for torsade de pointe and because pregnant patients can often be prescribed other QTc-prolonging medication(s). Examples include ondansetron and metoclopramide, used for nausea and vomiting of pregnancy, and haloperidol and quetiapine, used to treat comorbid psychiatric conditions. Up to 33% of pregnant patients with OUD have been reported to have comorbid psychiatric conditions, but this statistic may be low compared to practice.[71] As a result of the risk methadone poses for prolonging QTc, many providers obtain a baseline electrocardiogram, but there is debate in the literature on whether this should be done.[72] Notable maternal side effects of buprenorphine include mild, self-limiting nausea and constipation. Unfortunately, this can exacerbate nausea, vomiting, and constipation associated with pregnancy. There is less risk of respiratory depression and overdose with buprenorphine compared to methadone because of its partial mu-opioid agonist properties, and some data suggest that fewer pregnant people use illicit substances at delivery when treated with buprenorphine compared to methadone.[36]

Treatment logistics and convenience are often important to pregnant patients who have competing childcare, school, and occupational responsibilities. As with non-pregnant people, methadone requires initial daily clinic visits at an opioid treatment program (OTP), with the potential to earn take-home doses. Buprenorphine treatment can be managed through either an OTP or any clinic with a Drug Addiction Treatment Act of 2000 waivered provider.[21] The latter option may make buprenorphine treatment more feasible for some patients. However, some patients may prefer OTPs, which have extensive wrap-around services such as counseling and case-management, even though they require more frequent visits. Regardless of whether a patient chooses to start buprenorphine or methadone, no extra fetal monitoring, more intensive prenatal care than is standard, nor referral to a maternal fetal medicine specialist is necessary.[63] Hospitalization for MAT inductions is also unnecessary, although it may be preferred by some providers.[22]

Breastfeeding

Breastfeeding benefits are well established (Box), and many pregnant people affected by OUD wish to breastfeed upon delivery.[22] Numerous internationally recognized maternal and child health organizations recommend a postpartum person not breastfeed while actively using illicit substances in order to prevent neonatal exposure through breastmilk.[63] Although when not to recommend a new mother with OUD breastfeed is controversial, the Academy of Breastfeeding Medicine recommends a postpartum person not breastfeed if any of the following conditions are met: illicit substance relapse in the 30 days prior to delivery, a confirmed positive urine toxicology screen at delivery, failure to enroll and/or engage in treatment for substance use disorder, or any medical condition(s) contraindicated in breastfeeding.[73] However, breastfeeding is recommended for people being treated with methadone or buprenorphine for OUD[22] because of a lower incidence of NAS,[4,34] potentially reduced neonatal hospital stays, and less need for and amount of treatment.[23,58]

Case Continued

Lilly presents to a follow-up prenatal visit and antenatal testing at 30 weeks and 4 days gestation. She has had several prenatal visits, some of which involved a buprenorphine induction. Lilly chose buprenorphine because the treatment logistics and neonatal outcomes related to NAS were most important to her. She was previously diagnosed with preeclampsia and is now taking labetalol 400 mg by mouth twice daily. She also takes a prenatal vitamin by mouth and buprenorphine 32 mg SL once daily, and her sertraline dose was increased a few

TABLE 2: Possible false positive urine drug test immunoassay results for common medications used in pregnancy[75,76,77]

Commonly Prescribed Medications in Pregnancy	False Positive Substance of Abuse				
	Amphetamine/ Methamphetamine	Benzodiazepine	Barbiturate	Phencyclidine	Methadone
Bupropion	X	...	...	...	...
Dextromethorphan	...	...	...	X	...
Diphenhydramine	...	...	...	...	X
Doxylamine	...	...	...	X	X
Fioricet/Fiorinal	...	...	X	...	...
Labetalol	X	...	...	...	...
Metformin	X	...	...	...	...
Promethazine	X	...	...	...	...
Quetiapine (≥125 mg)	...	...	...	...	X
Ranitidine	X	...	...	...	...
Sertraline (≥150 mg)	...	X	...	...	...
Trazadone	X	...	...	...	...
Venlafaxine	...	...	...	X	...

weeks ago to 150 mg. A physical exam reveals normal vital signs, an uneventful fetal nonstress test, and appropriate weight gain. Per patient report, she has started having opioid cravings at night, is worried about relapsing, and would like to increase her buprenorphine dosing. Additionally, a previous urine toxicology screen reveals a preliminary positive result for methamphetamines and benzodiazepines.

Substance Screening in Pregnancy

Substance use screening is recommended for all pregnant people and a urine toxicology test using immunoassays is most commonly used.[8] Unfortunately, both false positive and negative results can occur and subsequently lead to negative consequences, including punitive measures. The ACOG recommends treatment over punishment because punishment does not end in improved maternal morbidity or mortality, creates barriers to care, and can result in unintended maternal and fetal withdrawal with its subsequent risks if a pregnant individual is placed in jail without treatment.[74] Initial screens are, therefore, presumptive until confirmatory testing is completed. Table 2 lists common medications taken during pregnancy that can result in false positive tests. Lilly tested positive for methamphetamines and benzodiazepines, but a review of her current medications indicates labetalol and an increase in sertraline dose may be the respective causes.[75-77] If confirmatory testing finds the benzodiazepine result accurate, continued treatment of Lilly's OUD would still be important and is recommended by the FDA even though she would be at an increased risk of respiratory depression.[78] Close monitoring, support, evaluation for a benzodiazepine use disorder, and a possible benzodiazepine taper or discontinuation would be appropriate.

Dosing Modifications

Although induction protocols need no modification in pregnancy, the dosing and frequency of both buprenorphine and methadone often need adjustment as a pregnancy progresses, especially during the second and third trimesters. The unique physiological changes that make modifications necessary are outlined in the Box. These changes result in lower buprenorphine and methadone plasma concentrations, shorter half-lives, and accelerated drug clearances.[79-84] Buprenorphine, specifically, is highly lipophilic, 96% bound to plasma proteins, and metabolized by the liver via the cytochrome P450 enzymatic pathway.[85] Buprenorphine, therefore, has significant pregnancy-specific pharmacokinetic alterations. Biophysical changes later in pregnancy have been shown to reduce buprenorphine plasma concentrations below 1 ng/mL, which is the theoretical concentration required to prevent withdrawal symptoms. This plasma concentration reduction can occur for 50 to 80% of a maintenance 12-hour dosing interval.[86] Lilly's cravings are more than likely due to a reduction in buprenorphine plasma levels along with an increased clearance and volume of distribution.[83,84,87]

Throughout pregnancy, the dilemma arises on how best to alter MAT dosing and frequency to account for the pharmacokinetic changes that occur. For buprenorphine specifically, studies[2,88] indicate a *ceiling effect* at doses above 32 mg per day in nonpregnant people; however,

optimal dosing in pregnancy has not been established and some pregnant patients require dosing up to 48 mg per day in practice. Furthermore, nonpregnant patients with OUD have higher opioid abstinence rates when treated with doses of 16 to 32 mg per day,[45] which makes treating pregnant patients with even higher doses logical and reasonable. Many pregnant patients also report needing divided dosing to 2 or 3 times daily in order to prevent withdrawal and cravings.[2] Divided dosing is thought to sustain plasma levels above the 1 ng/mL threshold throughout the day.[86] Since Lilly is experiencing opioid cravings at night, it is reasonable to consider dividing Lilly's daily buprenorphine to an AM and PM dose and titrate each based on symptoms and cravings.

Although Lilly is not treating her OUD with methadone, it is important to know that similar to buprenorphine, many pregnant people treated with methadone also report needing increased dosing and/or divided dosing to twice daily and, rarely, 3 times daily or every 6 hours as the pregnancy progresses.[23] The highest dosing this author has seen in pregnancy was 220 mg by mouth twice daily. Another patient, whose methadone trough levels were those typically seen with dosing of 120 mg daily, was taking 125 mg by mouth 3 times daily. Evidence suggests symptomatic patients may benefit from divided dosing if their methadone plasma trough level is under 0.3 mg/L because levels greater than or equal to 0.24 mg/L have been shown to prevent withdrawal in pregnancy.[80] Therapeutic drug monitoring is not empirically necessary for pregnant patients but is reasonable to aid in determining if a dose increase is needed. Of note, methadone dosing should not be titrated faster during pregnancy even with the pharmacokinetic changes that occur.

For methadone specifically, there are neonatal and maternal positive outcomes that occur with an increase in dose and frequency. When compared to a once daily large dose, these adjustments result in less maternal withdrawal and illicit opioid use, lower NAS severity, and a reduction in fetal exposure to repeated withdrawal periods.[79,89,90] Additionally, more methadone crosses the placenta as pregnancy progresses and sustained cord blood levels reduce periods of fetal withdrawal from pregnancy pharmacokinetic changes.[82] Although the clinical significance is unknown, divided methadone dosing results in less suppression of fetal movement and respiration than once daily dosing.[91,92] Optimal maternal buprenorphine dosing related to fetal effects has not been studied.

Upon delivery, the body's pharmacokinetic profile returns to a prepregnancy state over an average of 6 to 8 weeks. For example, hepatic function returns to baseline by approximately 6 weeks postpartum,[93] and plasma levels of buprenorphine are higher during the postpartum period due to a reduction in clearance.[87] As a result, doses and frequencies of both buprenorphine and methadone likely need to be reduced after delivery. These adjustments may be needed right away or as late as 12 weeks postpartum.[93] The patient and care team should be attentive to evidence of sedation to prevent MAT overdose; however, in order to prevent relapse, MAT should not be tapered too quickly. The stress of motherhood and sleep deprivation can put a new mother at risk for relapse, which happens most frequently between 3 and 6 months postpartum.[2] Close follow-up and support are critical. During her postpartum follow-up, Lilly will more than likely need her buprenorphine tapered to a lower once daily dose along with strong support.

Case Continued

Lilly, who is now 36 weeks and 2 days gestation, presents to a scheduled preoperative anesthesia clinic to be evaluated for optimal pain control for an expected vaginal delivery. A physical exam reveals normal vital signs, but she endorses anxiety about experiencing pain during labor and delivery and postpartum. She also reveals a concern about relapsing if she takes more opioids during her postpartum recovery. Lilly remains on sertraline, labetalol, and a prenatal vitamin, but her current buprenorphine regimen is now 20 mg SL every morning and 18 mg SL at bedtime.

Labor and Delivery Pain Control Options

Labor and delivery can be painful, which many pregnant people fear. Those with OUD are also hyperalgesic and often require more opioid analgesics at higher doses.[63] For example, pregnant patients taking methadone experience increased pain and can require up to 70% more opioids than nonMAT patients if a cesarean delivery is needed.[94] The hyperalgesia and increased analgesic requirements make pain control challenging. Therefore, the goal for this phase of pregnancy, aside from a successful birth, is to provide adequate pain control while preventing withdrawal, analgesic side effects, and overuse of opioids.

Lilly is appropriately concerned about her experience of pain and risk for relapse. She should be counseled that all patients experience pain differently and reassured that her providers will work to provide her with adequate pain control. Lilly should also be counseled that she is opioid-tolerant, may be hyperalgesic, and may require more analgesics for pain control but that there is no way to predict the extent of pain she will experience nor the amount of pain control she will need. Methadone and buprenorphine can be used to treat chronic pain; however,

a MAT home regimen will not provide adequate pain control for an acutely painful event. Lilly's buprenorphine dosing regimen should be continued throughout labor and delivery, and additional opioids and other analgesics may be given during labor and delivery and prescribed on discharge for pain control.[22] In practice, a 7 to 10 day supply of opioids are prescribed to postpartum patients at discharge when non-opioid analgesics are insufficient at controlling pain for a specific patient. Lilly should also be reassured that there are no data to indicate using opioids for acute pain leads to higher relapse rates.

Because of buprenorphine's partial mu-opioid agonist properties, many providers worry about precipitating withdrawal or difficulty controlling pain by continuing a home regimen while a patient is in acute pain. Animal studies, human data, and experience have proven this incorrect and that a home buprenorphine regimen can be synergistic when given with opioids for acute pain.[23,95] A recent study[95] demonstrated baseline buprenorphine dosing does not interfere with opioid pain management after cesarean section and there is no statistically significant difference in postoperative complications nor length of hospital stay for patients taking full buprenorphine dosing when compared to those not taking buprenorphine. Furthermore, discontinuing buprenorphine or reducing the dose exposes a new mother with OUD and the offspring to risks associated with withdrawal and maternal relapse and discomfort during a subsequent repeat induction. Some anesthesiologists and obstetricians recommend reducing a patient's dose down to 8 mg SL daily several days before a scheduled cesarean to allow for better pain control during and after the procedure; however, this has not been proven to facilitate adequate pain control and puts a patient at risk for relapse from uncontrolled cravings. The current recommendation for labor and delivery is to continue a home regimen for OUD whether buprenorphine or methadone is being used for treatment.[2,96]

Pregnant people often prefer to know their pain control options before going into labor, and Lilly should be counseled on what options may work best for her during this clinic appointment. General options are stated in the Box.

Other Aspects of Peripartum Care

After delivery, Lilly is at an increased risk of developing postpartum depression (PPD), a condition with significant morbidity and mortality that puts a patient at risk for relapse and should be monitored for and addressed.[97] In the general population, about 25% of postpartum people seek treatment for PPD whereas up to 45% of OUD patients screen positive for PPD and up to 40% of patients attending an OTP report having PPD.[22,23] This increase is compounded by co-occurring mental health disorders found in two-thirds of pregnant people with OUD.[66,98] Lack of sleep, stress from motherhood, and caring for a newborn all put this population at risk for PPD and subsequent relapse.[2] During each follow-up prenatal and postpartum clinic visits, Lilly should be screened for PPD and educated about PPD signs and symptoms and when to seek help.

Although Lilly is in a monogamous relationship and does not inject illicit substances, a thorough history should be taken at every prenatal visit to identify any behaviors putting her at risk for contracting human immunodeficiency virus. If a patient is at risk, pre-exposure prophylaxis may be considered and should be offered.[99]

Conclusion

Data and experience have shown that untreated OUD during pregnancy negatively impacts the pregnant person, fetus, and subsequent child. Fortunately, pregnant people affected by OUD are often motivated to enter and remain in care for the benefit of their current and unborn child(ren). As discussed, there are several treatment options that mitigate these consequences and are safe in pregnancy. Methadone and buprenorphine are first-line options and have demonstrated positive birth outcomes. Making a medication choice is multifactorial, and physiological changes of pregnancy present unique dosing challenges. Ideally, the major goal for OUD in pregnancy is successful and sustained maternal engagement in care during the antepartum and long after the postpartum period.

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