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Evaluation and Management of Opioid Dependence in Pregnancy

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Abstract

Background—Opioid use disorders are a growing public health problem in the United States. Most women who are opioid dependent are of childbearing age and management of opioid dependence during pregnancy poses unique challenges. Assessment includes evaluation for addiction, withdrawal syndromes, and co-morbid psychiatric diagnoses. Consultation-liaison psychiatrists may also be involved in acute pain management, perinatal medication management, buprenorphine induction and stabilization. For the past four decades, the standard of care has included methadone maintenance, but the increasing use of buprenorphine creates new treatment issues and opportunities.

Objective—To educate consultation-liaison psychiatrists in emergency and obstetrical settings about the appropriate approach toward the evaluation and basic management of women with opioid dependence in pregnancy.

Method—The authors reviewed the consensus literature and all new treatment options on opioid dependence during pregnancy.

Discussion—In this review, the authors summarize known and emerging management strategies for opioid dependence in pregnancy pertinent to consultation-liaison psychiatrists.

Background

Opioid use disorders are a major public health problem in the United States and nearly 90% of all American female opioid users are of childbearing age.[1] National surveys suggest that up to 4.4% of pregnant women ages 15–44 reported non-medical use of prescription opioids within the past year and even higher rates (15%) among pregnant teenagers ages 15–17

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years old.[2] Actual prevalence rates of non-medical use of opioids during pregnancy may be higher though difficult to establish due to underreporting.

Pregnant women with opioid dependence are less likely to engage in prenatal care, have higher rates of obstetric problems, and their neonates are at risk of multiple medical complications.[3–5] Challenges in the management of this patient population include the medical risks of illicit substance use in pregnancy, psychological comorbidity, and the psychosocial stressors that frequently interfere with prenatal treatment and addiction recovery. Despite these obstacles, pregnant women can be highly motivated to reduce substance use and most women strive for healthier pregnancy, providing a unique window of opportunity for intervention in this population.[6] Prior studies suggest that pregnant women struggling with addiction not only attempt to reduce their substance use, they also seek improved nutrition, sleep, and other life-style changes.[7]

Treatment of opioid use disorders during pregnancy is unique among other types of substances because of its long record of favorable maternal and neonatal outcomes.[8] The availability of replacement therapy shifts the emphasis from an abstinence-only model to that of harm reduction and engagement in treatment. While the standard of care for opioid replacement therapy in pregnant women remains methadone, buprenorphine is now also a viable treatment option.[5]

This review will cover the evaluation and management of the opioid-dependent pregnant woman and will pay special focus on the use of buprenorphine due to emerging data showing its comparable efficacy and safety during pregnancy and decreased severity of fetal withdrawal symptoms.[9] While other emerging treatment options for opioid dependence such as oral or intramuscular naltrexone are available, they will not be covered in this paper due to the lack of substantial safety data in pregnancy.

Definitions

Opioid use disorders are heterogeneous in nature, ranging from lower risk substance “misuse” problems to addiction. Addiction is a concept not defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) and is characterized by a loss of psychological control and continued use of substances despite consequences.[10] The DSM-IV-TR defines substance dependence as a maladaptive pattern of substance use leading to clinically significant impairment along with tolerance and/or withdrawal following cessation of use.[11] The DSM-IV-TR also defines substance abuse as a maladaptive pattern of repeated use leading to interpersonal problems or danger to self.[11] Patients who engage in opioid misuse, non-medical opioid use, and aberrant drug taking encompass a larger population of people who may or may not meet criteria for DSM-IV-TR substance abuse or dependence.

Medical risks of opioids in pregnancy

As compared to other substances, the physiologic negative effects of opioid use during pregnancy are less clear.[3] Intermittent therapeutic use has not demonstrated significant negative impact on maternal health. Oral opioids such as oxycodone are frequently prescribed for pain during pregnancy and delivery. Data on the teratogenic effects of opioids

are inconsistent and exposure to opioids during the first trimester may be associated with elevated risk of fetal congenital heart defects.[12]

Heavy, chronic opioid use is associated with increased rates of prematurity, intrauterine growth retardation, preeclampsia, spontaneous abortion and intrauterine death (see Table 1 for risks of chronic opioid use on pregnancy outcomes).[4] The cycle of repeated opioid intoxication and withdrawal leads to unstable serum levels of the opioid and increased fetal activity.[13] Intravenous opioid use exposes the mother and fetus to risks of infectious diseases such as Human Immunodeficiency Virus (HIV) and hepatitis B and C.

Interestingly, many of the dangers associated with opioid use disorders may be due to the maladaptive behaviors resulting from the addiction. Women addicted to opioids are less likely to seek prenatal care and are more likely to contract infectious diseases and be in violent relationships.[3, 4] They may be more likely to discover pregnancy later in gestation and are at higher risk of unplanned pregnancy.[14] Furthermore, heroin use can disrupt the menstrual cycle, a phenomenon that may be reversed with methadone or buprenorphine stabilization and may increase the risk of unintended pregnancy during early recovery.[15]

For the pregnant opioid dependent patient, including those participating in opioid-maintenance treatment, polysubstance use (most commonly nicotine, alcohol, benzodiazepines, cocaine) is prevalent.[14, 16, 17] Isolating the teratogenic effects of any one substance is difficult as they are frequently taken in combination.

Evaluation for co-morbid psychiatric conditions

Pregnancy and the postpartum are periods of heightened sensitivity to psychiatric disorders which may complicate treatment of substance abuse.[18] Between 56–73% of opioid dependent pregnant women have a co-morbid psychiatric disorder.[19] Substance-abusing women are at higher risk for psychological distress than their non-using counterparts, and untreated axis I disorders in these women are associated with poorer maternal outcomes.[20] There are limited data on recommended treatments of psychiatric disorders in pregnant women with co-morbid opioid dependence. However, the authors of this article recommend concurrent management of psychiatric symptoms with treatment of the substance use disorder.[21]

When evaluating opioid-dependent pregnant women, clinicians should employ broad screening for all psychiatric disorders as previous studies have suggested elevated rates of multiple conditions in these women including depressive disorders, anxiety disorders, post-traumatic stress disorder, and hypomania.[18, 20]

As with all pregnant women, clinicians must weigh the potential risk of psychopharmacologic intervention on fetal exposure with the benefits of reduced psychiatric illness and symptom burden. Pharmacologic interactions with methadone and buprenorphine must be considered when making medication choices, though a discussion of the specific use of psychotropic medications during pregnancy is outside the scope of this paper. In addition, non-pharmacologic approaches such as psychotherapy should be encouraged.[18]

Following initial evaluation, every effort should be made to refer the opioid dependent pregnant women to a specialized pregnancy and addiction treatment program. Female substance users have higher rates of poverty, unemployment, and current and prior physical and sexual abuse.[22] Their greater burden of psychosocial stressors is best supported by treatment within a multidisciplinary center with intensive social services support.

Management of opioid withdrawal

Opioid withdrawal manifests as autonomic, neurologic, and influenza-like symptoms, many of which can be confused with symptoms of normal pregnancy.[23] Careful differentiation of these symptoms is needed to appropriately avoid and manage symptoms of withdrawal during pregnancy. In adults, opioid withdrawal is distinctly uncomfortable but not fatal. For fetuses and neonates, abrupt opioid reduction was historically associated with greater central nervous system stress,[24] stillbirth,[25] and rarely, death,[4] although more recent data suggests that gradual opioid detoxification within a treatment center is not associated with worse fetal outcomes.[26, 27]

Management of Detoxification

Most opioid dependent women should be maintained on opioids during pregnancy. Detoxification is not routinely recommended by leading experts, such as researchers at the Center for Addiction and Pregnancy at the Johns Hopkins Bayview Medical Center, due to the high risk of drug relapse.[21, 27] Opioid detoxification is also associated with risk of precipitating fetal distress[24] and co-morbid alcohol or sedative/hypnotic dependence can greatly complicate withdrawal management. Most opioid-dependent women who present during pregnancy are referred to opioid maintenance therapy instead of detoxification but rates of referral for opioid maintenance treatment versus controlled detoxification are unknown.

In limited circumstances, opioid detoxification may be appropriate for the highly motivated patient with a strong preference to remain drug-free. In such instances, the safest option may be to refer these patients to specialized opioid detoxification treatment centers. Women with greater social support and access to residential treatment may be less likely to resume illicit opioid use although detoxification in these patients has not been adequately studied.

When indicated, opioid detoxification is recommended by the American Society of Addiction Medicine during the second trimester[28] to avoid risk of miscarriage associated with first trimester withdrawal[5, 27, 29] and potential risk of precipitating preterm labor after the 32nd week of gestation.[6] Recent studies in women with uncomplicated pregnancies have demonstrated the safety of gradual detoxification with methadone or clonidine in highly monitored inpatient settings.[26, 27] Although no standard protocols exist for opioid detoxification during pregnancy, the Center for Substance Abuse Treatment (CSAT), of the Substance Abuse and Mental Health Services Administration (SAMHSA), recommends methadone tapers of 1.0 to 2.5 mg per day for inpatients and by 2.5 to 10.0 mg per week for outpatients.[30]

Pharmacologic Management with Methadone

The primary pharmacologic treatments for opioid dependence are methadone and buprenorphine. The National Institutes of Health Consensus Development Panel currently recommends methadone treatment offered through federally regulated clinics as the standard of care for pregnant women seeking opioid maintenance.[21]

Treatment with methadone has demonstrated reduced pregnancy complication, higher birth weights, decreased HIV risk behaviors, decreased crimes rates and improved adherence to prenatal care when provided as part of a comprehensive care program.[4, 21, 31] In addition, the long half-life of methadone (24–36 hours)[26] helps ensure consistent blood levels in the fetus.

For most pregnant women, methadone doses between 80–120mg per day are sufficient and equivalent to non-pregnant patients, though some women may require dosage adjustments during pregnancy.[4] Progesterone enhances cytochrome p450 metabolism of methadone which leads to increased methadone clearance and decreased opioid levels during the third trimester when progesterone and estrogen levels are significantly elevated.[23, 32] Decreased oral absorption, expanded volume of distribution, and reduced plasma protein binding during pregnancy may also contribute to reduced methadone levels during later pregnancy.[33] Dosage increases or split dosing may be necessary to avoid precipitation of cravings or withdrawal.

Pharmacologic Management with Buprenorphine

Recently, buprenorphine has emerged as an alternative to methadone due to its availability in office-based settings, shorter duration and lessened intensity of neonatal withdrawal, and unique pharmacologic properties.[6, 21] Buprenorphine is a partial mu-opioid receptor agonist and kappa-opioid antagonist with a long half-life of 24–60 hours.[34] Induction with buprenorphine is more complicated than methadone due to the potential risk of precipitating withdrawal. Most non-pregnant patients are stabilized on daily doses of 4–24mg, though no guidelines exist on appropriate doses during pregnancy.[21, 35] Unlike methadone, treatment with buprenorphine is less likely to require dosage adjustments during pregnancy, though the mechanism for this remains unknown.[21] Transitioning from methadone to buprenorphine is possible though not routinely recommended.[36]

SAMHSA recommends buprenorphine monotherapy (Subutex®) instead of Buprenorphine/Naloxone (Suboxone®) for pregnant women due to the lack of controlled studies using Suboxone. Jones et al. recommend avoidance of Suboxone to reduce risk of teratogenicity associated with naloxone, which may produce changes in maternal luteinizing hormone.[21] In addition, inappropriate use of Suboxone via injection could precipitate opioid withdrawal due to the intravenous bioactivity of naloxone.[35] Women who conceive while on Suboxone replacement therapy should be switched to Subutex for the duration of the pregnancy, despite the potential increased risk of medication misuse.[21, 35] Several studies have revealed small numbers of pregnancies conceived during low dose (6–12mg/day) buprenorphine maintenance therapy without complications.[37]

Initial studies of buprenorphine demonstrated its safety and tolerability in pregnancy,[38, 39] but studies directly comparing methadone and buprenorphine treatment were limited by small sample sizes or open label design.[40–43] To address this, researchers at Johns Hopkins and across 8 international sites conducted the Maternal Opioid Treatment Experimental Research (MOTHER) trial, a double-blind, double-dummy, randomized controlled trial of 175 pregnant women comparing buprenorphine with methadone for the treatment of opioid dependence in pregnancy through 28 days postpartum. There were no differences in maternal outcomes – including caesarian section rates, study discontinuation, anesthesia, and medical complications – between the two groups.[9] Study outcomes related to the development and presentations of fetal withdrawal symptoms are discussed in the next section below. There was a higher rate of subject dissatisfaction with buprenorphine – a phenomenon that may have been related to the low induction doses of buprenorphine.

Neonatal abstinence syndrome and fetal risks of opioid treatment

Opioid maintenance treatment is not without risk. The most significant adverse effect associated with both methadone and buprenorphine treatment is fetal withdrawal. Other side effects associated with treatment include alterations in fetal activity and heart rate[21, 44] as well as intrauterine growth restriction.[45] The consequences of opioid-induced changes in fetal activity and heart rate are not well known.

Longitudinal studies of prenatal heroin or methadone exposure on infant developmental outcomes have yielded conflicting results.[22] Differentiating the opioid effects from confounding factors has shown to be challenging in this clinical population. In addition, individual opioids have different affinities for receptors and receptor subtypes (e.g. methadone affects mu-opioid receptors as well as NMDA receptors), making comparisons between opioid exposures difficult.[46, 47] Some studies demonstrate long-lasting depressed psychomotor performance and behavioral abnormalities detected at school age[48–50] while other studies show much less severe outcomes, especially when comparing children from similar socio-economic groups.[51] Animal models suggest neurobehavioral deficits can occur even without overall developmental retardation.[52]

When reviewing the pharmacologic options, clinicians should inform patients that long-term studies of prenatal exposure of buprenorphine are in progress and there are fewer data relative to methadone. Table 2 provides additional information about fetal risks of methadone and buprenorphine exposure as compared to heroin. Further research should include a meta-analysis directly comparing outcomes on retention, relapse, and neonatal abstinence syndrome (NAS) between maintenance therapies, including buprenorphine, and no treatment.

Chronic exposure to any opioid during pregnancy can result in the development of NAS, a constellation of symptoms affecting the newborn’s central and autonomic nervous system that can occur hours to days following delivery.[9] Symptoms of NAS include irritability, tremor, hypertonicity, vomiting, diarrhea, excessive crying, and rarely, seizures.[53] Witnessing these symptoms can be distressing for the parents. Involved clinicians can help

by educating and supporting the mother as well as Neonatal Intensive Care Unit (NICU) staff about these symptoms to help facilitate the mother's involvement in her infant's care.[16]

There is an unclear relationship between the severity and duration of NAS and methadone or buprenorphine dosage, though most infants will demonstrate at least some symptoms.[16, 17] NAS is also observed in response to withdrawal from other psychotropic substances such as benzodiazepines.[3] Infants at risk of opioid-induced NAS frequently require NICU-level care and regular monitoring of opioid withdrawal symptoms.[53] Common pharmacologic treatments of NAS include tincture of opium, morphine sulphate solution, or methadone.[53]

The MOTHER trial found that buprenorphine treatment resulted in a significant reduction in the severity and duration of NAS, compared to methadone treatment. The overall proportion of infants who developed NAS symptoms requiring opioid treatment (47% vs. 57%) did not differ between groups, nor did peak NAS scores differ significantly between the two treatment arms. However, infants exposed to buprenorphine required 89% less morphine (1.1mg vs. 10.4mg) and spent on average 43% less time in the hospital (10.0 vs. 17.5 days) and 58% less time receiving treatment for NAS.[9]

Labor & Delivery Management

Maintenance doses of methadone and buprenorphine do not provide adequate analgesia for labor pain.[54] To avoid precipitating withdrawal, these medications may be continued during labor and delivery.

Women receiving opioid agonist treatment usually report elevated pain scores and demonstrate greater opioid requirements than substance-abusing women not maintained on opioids or a normal, control group.[55, 56] In one study, women prescribed buprenorphine had 50% higher opioid requirements (89.3mg Oxycodone equivalents vs. 60.9mg) following cesarean delivery compared to control patients without opioid dependence.[55]

Acute peripartum pain in the opioid-maintained patient can be safely treated with additional short-acting opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Although buprenorphine's pharmacology as a partial mu opioid-receptor agonist can potentially complicate acute treatment of pain, preliminary data supports the use of continued buprenorphine with adjunctive opioids for pain control during the peripartum period. Several small studies indicate that postpartum pain following vaginal delivery can be adequately managed using NSAIDs and oxycodone for breakthrough pain with typical doses.[55, 57] In another study of both methadone and buprenorphine-maintained patients, the brief administration of morphine or acetaminophen with codeine was well tolerated in both groups.[40] Most of these studies were limited by the absence of control groups. Buprenorphine can also be discontinued and pain treated with full opioid agonists, but stopping this medication does require re-induction when acute pain has resolved if the patient wishes to resume treatment. There are no studies that suggest that the brief use of additional opioids in the postpartum period in an opioid-maintained patient interferes with her recovery from addiction.

Use of regional analgesia such as epidural opioid anesthesia is an acceptable method of pain control, and is preferable to systemic opioid analgesia.[1] To avoid the risk of precipitating withdrawal during labor, the high-affinity, partial opioid agonists such as nalbuphine (Nubain) should not be used if the patient is using lower-affinity full agonists such as methadone.[58] When possible, developing a plan for pain management with the anesthesiologist prior to delivery is preferable.[1]

Following delivery, these women are at high risk of drug relapse. The prevalence of illicit drug use in new mothers is roughly equivalent to rates in non-pregnant women.[2] Given the risk for relapse, further research and programs devoted to supporting women and stabilizing the postpartum home environment is needed.

Breastfeeding

Breastfeeding has multiple health benefits for infants and mothers.[21] Breastfeeding with methadone is encouraged when the patient is HIV-seronegative and not abusing other substances and may even help ameliorate some symptoms of neonatal withdrawal.[21, 58] The amount of methadone exposure in breast milk appears to be low and without direct correlation to maternal methadone dose.[21] Breastfeeding with buprenorphine is also encouraged, though long-term data are lacking. Buprenorphine has poor oral bioavailability and the nursing infant is exposed to only 10–20% of total available drug.[35] Therefore breastfeeding exposure to buprenorphine is unlikely to affect NAS.[19, 21]

Treatment resistance

Women who cannot remain abstinent from substances of abuse, despite knowledge of the potential harm to the fetus, represent a group with severe addiction. Treatment resistance can pose a major challenge in psychiatric evaluation and treatment. Expecting these women to remain abstinent for the duration of their pregnancy may be unrealistic and counterproductive.[13] Stigmatizing or shaming patients during this time is harmful and will further increase resistance to treatment. Pregnant women experience greater rejection, blame and stigma than other populations with similar levels of substance use.[59]

Women’s fear of negative judgment as well as fear of prosecution can serve as a major barrier to care. When a pregnant woman admits to misusing or abusing substances, she is taking a major step towards treatment. Acknowledging the efforts that women take toward healthy behaviors is vital, especially when evaluating her in the emergency or medical settings. Empathic attitudes and facilitating treatment entry are among the primary goals of the consultant. Recognizing counter-transference and anticipating treatment-interfering behaviors can help not only the consultation-liaison psychiatrist, but also the obstetrical team when working with these patients. Strategies utilizing motivational interviewing or contingency management have also had some success with treatment engagement in this population though more research is needed.[60]

Legal issues

Treatment of opioid-dependent pregnant women raises multiple ethical and legal questions for providers, particularly when the mother's actions compromise the health of her pregnancy. Issues of confidentiality and patient autonomy become important aspects of the clinical encounter with these patients. Substance abuse testing and reporting laws for pregnant and postpartum women widely vary across the United States. Providers should have a clear understanding of their states laws and be prepared to discuss this with their patients. Fifteen states consider prenatal substance use child abuse and grounds for termination of parental rights.[61] Three states can authorize civil commitment of prenatal users and mandate drug treatment.[61] Misunderstanding about state policies may impede the patients' willingness to openly discuss their substance use and engage in treatment.

Conclusions

Consultation-liaison psychiatrists should be knowledgeable about the acute evaluation and management of the opioid dependent pregnant patient. Goals of treatment include reducing fetal exposure to illicit substances, stabilizing the mother and fetus' environment, avoidance of opioid withdrawal and increasing engagement in prenatal treatment. In contrast to the clinical management of other substances of abuse, abstinence is not the goal of treatment for the pregnant opioid dependent patient due to the high risk of relapse as well as the potential medical risks of opioid detoxification during pregnancy. Buprenorphine has emerged as a new and effective alternative to methadone maintenance treatment and represents an increasingly valuable option in the management of this population.

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Table 1

Risks of opioid dependence during pregnancy

Effects of opioid dependence on pregnancy outcomes	Confounding factors associated with opioid dependence in pregnancy
Spontaneous abortion	Poor nutrition
Preeclampsia[29]	Intimate partner violence
Intrauterine growth retardation	Reduced prenatal care
Intrauterine death	**Polysubstance use**
Preterm birth	Co-morbid psychiatric illness
Low Apgar scores[4]	Infection (esp. with intravenous use)
Intrauterine passage of meconium[4]	Inadequate housing
Placental insufficiency[29]	Poverty
Premature rupture of membranes[29]	Poor dental hygiene[4]
Neonatal abstinence syndrome	
Long-term neurobehavioral symptoms	

Table 2

Fetal effects of heroin as compared to methadone and buprenorphine

	Heroin	**Methadone (administered within a comprehensive program)**	**Buprenorphine (administered within a comprehensive program)**
Fetal pharmacokinetics	Rapid transplacental passage,[47] short half-life increases risk of fluctuating fetal opioid levels	Rapid transplacental passage,[47] longer half-life reduces risk of unstable fetal opioid levels	Rapid transplacental passage,[47] longer half-life reduces risk of unstable fetal opioid levels
Spontaneous abortion	High (estimated 10–20%)[23]	Moderate, estimated 3–4%[23]	Unknown, possibly less than methadone[23]
Decreased heart rate and heart rate variability	Present	Present, especially in third trimester[44]	Present, possibly less severe than methadone during first trimester[44]
Neonatal abstinence syndrome	Common, rapid onset usually by 24 hours[58]	More frequent than compared to heroin, often delayed onset >48 hours	Common, but less severe in intensity and duration than for methadone
Cognitive	Short and long-term neuropsychiatric effects present but multiple confounders[44]	Short and long-term neuropsychiatric effects present but multiple confounders[44]	Neuropsychiatric effects present but multiple confounders. No long-term available data yet[44]
Premature delivery	Increased risk, variable rates depending on confounding factors	Increased risk but less than heroin[43]	Increased risk but less than heroin, similar to methadone[43]
Impaired somatic growth	Decreased head circumference, birth weight and intrauterine growth restriction,[44] estimated relative risk of low birth weight is 4.61 compared to non-drug using mothers[6]	Present but less severe than heroin,[44] estimated relative risk of low birth weight is 1.36 compared to non-drug using mothers[6]	Present but less severe than heroin. Similar effects relative to methadone[44]
Reduced fetal motor activity	Present	Present, especially in third trimester[44]	Present, possibly less severe than methadone during first trimester[44]

Table 3

Management of Opioid Dependence in Pregnancy: Key Points

- Most pregnant women with opioid dependence are unable to maintain abstinence from substances during pregnancy
- Uncontrolled opioid withdrawal during pregnancy should be avoided due to risks to the fetus
- Buprenorphine is an effective alternative to methadone maintenance treatment during pregnancy
- Treatment with buprenorphine maintenance therapy is associated with decreased severity and duration of neonatal abstinence syndrome