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REVIEW ARTICLE

Current Research on Opioid Use Disorder (OUD) in Pregnancy with Emphasis on Medication Assisted Treatment (MAT)

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ABSTRACT

Substance use disorder in pregnancy is a major obstetric issue, with significant maternal and fetal morbidity and mortality. The incidence of opioid use disorder has risen substantially in the United States, with overdose now a leading contributor to pregnancy related deaths. Medication assisted treatment for opioid use disorder can improve pregnancy outcomes, with Methadone, and more recently Buprenorphine becoming the mainstays of treatment. There is decreased incidence of neonatal abstinence syndrome with maternal Buprenorphine use, as well as possible decreased association with neonatal low birth weight. Despite the known benefits of treatment, there remain barriers to medication assisted treatment, including clinician stigma and lack of familiarity with pharmacology. The American College of Obstetrics and Gynecology maintains a firm stance on the benefits of treatment during pregnancy, in order to avoid the known adverse outcomes associated with substance abuse during pregnancy. Pregnancy is period when most women routinely seek healthcare, and thus allows the opportunity for obstetrical providers to optimize maternal well-being. The goals during pregnancy remain the same as those outside of pregnancy: For medication treatment to assist in the prevention of a chronic and remitting condition that can result in overdose, and provide a gateway towards long-term recovery.

Introduction:

Substance use disorder (SUD) in pregnancy is a marked and often unrecognized complication that significantly worsens maternal and fetal outcomes. The incidence of opioid use disorder (OUD) has been increasing in the United States, with overdose now a leading contributor to pregnancy related deaths in the year following delivery[1]. Medication assisted treatment (MAT) for OUD has been shown to improve pregnancy outcomes, however its use has been limited by multiple factors including provider stigma, poor prescriber access and insurance barriers[2]. Previous studies have shown significant underutilization of these treatment options, with only 50-60% of pregnant patients with OUD on any medical management[3,4].

Despite the increasing incidence of OUD in pregnancy, few obstetricians or maternal fetal medicine physicians have experience managing and prescribing medication assisted treatment, and instead rely on addiction medicine practitioners. However, pregnant patients with SUD have known barriers to access, with a randomized field experiment showing that they are 17% less likely to be accepted for outpatient OUD treatment compared to identical non-pregnant women[2,5,6]. These numbers are even more alarming when the patients belong to a medically vulnerable group such as a person of color, residing in a rural location or have a language barrier[2,5].

In the United States (U.S)., the American College of Obstetricians and Gynecologists (ACOG) has unequivocally endorsed MAT as the optimal treatment for OUD in pregnancy, and considers it preferable to medically assisted withdrawal, as withdrawal is associated with higher rates of relapse and poorer outcomes[7]. Medication assisted treatment has been shown to reduce maternal relapse and mortality, and also improve pregnancy outcomes such as a reduction in preterm birth and low birth weight[1,2,7].

Further complicating care, is the noted medico-legal complexity in regards to prescribing MAT and management of these patients. Pregnant patients with SUD find themselves hesitant to seek care due to fear of being referred to state child welfare programs, with the potential for their child being removed and placed in the foster care system. Parental substance abuse is present in more than 50% of infant foster care placements, with this data being even more stark in ethnic minorities[1].

The U.S. Congress passed an omnibus bill in December 2022 that legislates significant changes in the legal prescription of buprenorphine in an attempt to reduce the barriers to patient access[1]. These changes warrant review and dispersal amongst the medical community. Pregnancy remains an ideal period during which healthcare disparities can be corrected, and patients can receive the psychosocial and medical treatment they require. All major public health entities recommend improved access to MAT therapy during pregnancy[3,7,8].

This review is intended to educate those who routinely provide obstetrical care information and an increased understanding into the scope of SUD in the pregnant population. Additionally, it is prudent for obstetrical providers to gain a more thorough understanding of the pharmacology of the medications typically used for the treatment of SUD, which can facilitate increased comfort with prescribing appropriate medications. Familiarization with the necessary counseling and psychological resources necessary to take for this patient population, in conjunction with medication management, can result is positive maternal, fetal, and neonatal outcomes.

Medications for Opioid Use Disorder during Pregnancy:

The misuse of alcohol and drugs among pregnant women has been reported in early medical literature[9]. This includes reports of infants born to opium-using mothers developing withdrawal symptoms requiring morphine for treatment[9]. The specific issues related to opium and heroin use during pregnancy and the post-partum period were increasingly reported into the 20th century[10]. There was a lack of knowledge in the management of addiction during pregnancy. Women who were heroin dependent had increased risk of toxemia, premature birth, and stillbirth. When women with heroin use were admitted for delivery it was clear that ignoring withdrawal symptoms led to early departure against medical advice[11].

Development of medications to assist in the treatment of women, women during pregnancy, and neonatal treatment of withdrawal syndromes has been a topic of much research in the last century and especially in the last twenty-five years as the opioid epidemic has increased to unprecedented levels. Although there are dependence and withdrawal syndromes related to several classes of medication, here we will focus on treatment of opioid use disorder[12–14].

Neurobiology and Pharmacology of Mu Receptor:

The pharmacology of the opioid receptor has been thoroughly studied and presented in the literature[15–18]. Opioid receptors are classified as Mu, Kappa and Delta. The pharmacology of medications for treatment of OUD is focused primarily on the Mu receptor. Mu receptor activity from exogenous opioids is responsible for supraspinal analgesia, sedation, euphoria, decreased gastrointestinal motility, tolerance and dependence[17]. The respiratory depression and apnea from opioid overdose is a result of activity on the Mu receptor along with reversal of the symptom when an antagonist such as naloxone is used[19].

In the U.S. the three Food and Drug Administration(FDA) approved medications for OUD include methadone, buprenorphine, and naltrexone extended-release (XR). Each of the medications has affinity for the Mu opioid receptor. Methadone and buprenorphine are routinely used for OUD during pregnancy while naltrexone-XR has been used less frequently.

Methadone:

Methadone is a full-agonist opioid and the first approved by the FDA to treat OUD. Proven benefits include reductions in relapse and overdose along with increased retention in treatment. As a full-agonist opioid methadone can lead to respiratory depression and apnea.

Methadone cannot be prescribed from an office-based setting but only dispensed from Opioid Treatment Programs (OTP) as outlined under Federal Guidelines. (SAMHSA Federal Guidelines 2015) The details of screening, pre-treatment testing, dosage initiation and adjustment have been outlined in SAMHSA TIP 63 including specific dosing issues during pregnancy such as split dosing. (SAMHSA TIP 63) Methadone was standard of care for OUD during pregnancy until the approval of buprenorphine treatment. The current use of MOUD during pregnancy is divided between methadone and buprenorphine[20–23]. Methadone is preferred treatment for OUD when an individual has failed buprenorphine induction attempt, had a relapse on buprenorphine, when higher doses are needed for symptom control, when access to methadone is readily available, and the need for daily monitoring to keep engaged in treatment[20].

Buprenorphine:

The FDA approved buprenorphine in 2002 for the treatment of OUD in an office-based setting. Buprenorphine benefits include reduction in illicit opioid use, reduced risk of fatal opioid overdose and improved retention in treatment. Prior to FDA approval, studies confirmed the efficacy and favorable outcomes when compared to methadone[24]. This was a significant change with increased opportunity to receive evidence-based treatment without the restrictions associated with an OTP. In the U.S. the initial regulations to prescribe buprenorphine required an approved 8-hour training for physicians to obtain a DEA 'X' waiver and limited the number of active patients to 30 in the first year. In December 2022, the Consolidated Appropriations Act (Omnibus Bill) was passed which removed the X waiver requirement and the limits on number of active patients.

Buprenorphine is a semi-synthetic partial agonist opioid. The pharmacodynamics and pharmacokinetics of buprenorphine have also been well-studied[16]. The buprenorphine naloxone combination therapy has been preferred to treat OUD. The buprenorphine mono product is commonly used during pregnancy and in individuals with documented side effects from naloxone. Although solo buprenorphine has routinely been used for OUD during pregnancy there has been no documented adverse effect from the buprenorphine naloxone combination[25].

Buprenorphine is administered sublingually in tablet form and the combination buprenorphine naloxone sublingually in film and tablet forms. The first extended-release subcutaneous form of buprenorphine was approved by the FDA in 2017, but use during pregnancy has been limited due to lack of larger studies[26,27].

Unlike methadone initiation, induction onto buprenorphine treatment from any full-agonist opioid requires the individual to be in opioid withdrawal. The buprenorphine partial agonist effect and the high affinity for the mu opioid receptor can induce precipitated withdrawal symptoms if an appropriate level of withdrawal is not present at the onset. The process of induction from prescription opioids such as codeine, hydrocodone, oxycodone, hydromorphone and illegal heroin is often accomplished without precipitated withdrawal when done with appropriate planning. However, as illicitly manufactured fentanyl has become the predominant opioid the induction process onto buprenorphine has become more complex. Due to precipitated withdrawal various buprenorphine induction plans have been researched and described such as standard dose, low dose, high dose, and microdosing. The details of each dosing regimen have been outlined in the medical literature. (PCSS Practice-Based Guidelines, 2023)

Since its approval in 2002 there has been a trend toward buprenorphine as the treatment of choice for OUD in pregnancy. Studies have shown efficacy, safety and improved neonatal outcomes when compared to methadone[21,22,28,29]. Providers of buprenorphine during pregnancy should be aware of dosage adjustment increase that may be required due to decreased plasma concentration and associated symptoms of withdrawal or craving[30]. The ability to provide buprenorphine in an office-based environment gives women an additional option for OUD treatment without the requirement for daily dose dispensing.

Although continuation of maintenance OUD during pregnancy has been preferred, studies have shown the option to taper can be done without increasing risk to mother or neonate. The importance of significant social services and behavioral health services for the mother during the taper and after delivery are necessary parts of a treatment plan[31–33]. In one study using a shared decision-making tool in women with OUD, 36% chose a taper option when given comprehensive information about the risk versus benefits of medications, risk of relapse and risk of NAS/NOWS[34].

Naltrexone:

Naltrexone (NTX) is a competitive mu opioid receptor antagonist. There are limited clinical trials on the use of naltrexone during pregnancy. Most clinicians who treat OUD in pregnancy with methadone or buprenorphine have minimal if any experience using naltrexone during pregnancy.

Naltrexone is administered orally in tablet form (50mg daily) or extended-release injectable (XR-NTX 380mg IM monthly). The XR-NTX has been the preferred route in treatment of OUD. The process of initiation of NTX requires a 7-10 day period off of all opioids including illicit opioids, prescription opioids, methadone and buprenorphine. Treatment of opioid withdrawal symptoms using non-agonist medications will be necessary. This is a high-risk window for relapse to opioid use and must be monitored closely especially in pregnant women. Once an individual is successfully on NTX the tolerance to opioid agonists is significantly decreased. If an individual discontinues NTX and relapses to opioid use, there is an increased risk of overdose. The decreased tolerance will put an individual at risk of overdose at an opioid dose which previously had been tolerated. Another concern for NTX treatment during pregnancy is pain management. As a mu receptor antagonist, the analgesic effect of opioids administered for pain control during labor and post-partum will be decreased. This is especially of concern if cesarean section is required for delivery. (SAMHSA TIP 63)

The latest SAMHSA TIP63 publication updated in 2021 advised against starting naltrexone during pregnancy. This recommendation was based on references from 2012, when methadone was the predominant medication used for OUD in this population. However, a survey study indicated a strong interest from pregnant women for naltrexone as an alternative treatment that was not associated with NAS[35]. Another small study looked at a retrospective cohort of 6 mother-infant dyads maintained on naltrexone (3 oral NTX and 3 XR-NTX injectable) compared to buprenorphine. The NTX treatment cohort had favorable pregnancy and infant outcomes without evidence of immediate complications. The authors did mention naltrexone should not be considered a first-line treatment[36]. A larger study of 121 mother-infant dyads on NTX compared to 109 on either methadone or buprenorphine had similar positive outcomes, no complications and no NAS in the 87 infants born to mothers who were on NTX up to delivery[37].

A national provider survey conducted in 2022 found half of the provider sites who offered naltrexone did not treat pregnant patients, and a significant barrier was the lack of national guidelines supporting naltrexone use in pregnancy[38]. Although the reported maternal and neonatal outcomes have been favorable, the need for larger multicenter trials will be important to determine longer term issues such as relapse risk post-partum, immediate and chronic neonatal risks such as neurocognitive function, and retention in treatment compared to methadone and buprenorphine[36,37,39–41].

Buprenorphine versus Methadone in Pregnancy

Buprenorphine and Methadone are dissimilar medications, despite both being used for OUD. Their mechanism of action, as described in detail above precludes easy substitution and the choice of medication to maintain the patient on, has to be determined after thorough evaluation of their candidacy for either regimen. Recent studies have evaluated for superiority of medication to be used in pregnancy, for both maternal and fetal outcomes.

The Maternal Opioid Treatment: Human Experimental Research (MOTHER) trial[29] published in 2010, was a randomized, double-blind trial that studied the difference in NAS between infants who had prenatal exposure to buprenorphine versus methadone. Of the 131 neonates exposed to MAT, the 58 exposed to buprenorphine required less morphine, had a significantly shorter hospital stay (10.0 days vs. 17.5 days) and duration of treatment for NAS (4.1 days vs. 9.9 days). No differences in serious maternal or neonatal adverse outcomes was noted. They did note in their study, that patients taking buprenorphine were more likely to discontinue treatment than the patients on methadone, with "dissatisfaction" with the study medication listed as primary reason.

To further answer questions regarding differences in outcomes between the two medications, a large cohort study was conducted utilizing nationwide Medicaid data from 2000 through 2018, and included over 2.5 million pregnancies[22]. NAS occurred in 52% of infants exposed to buprenorphine, as opposed to 69% in those exposed to methadone (adjusted relative risk, 0.73; 95% confidence interval [CI], 0.71 to 0.75. Interestingly, the authors also evaluated for and found marked reductions in the risk of preterm delivery for patients on buprenorphine as opposed to methadone, along with reductions in small size for gestational age and low birth weight in those neonates. They concluded that buprenorphine exposure in utero resulted in improved neonatal outcomes when compared to methadone exposure, with similar maternal outcomes.

Neonatal Abstinence Syndrome and Neonatal Opioid Withdrawal Syndrome

Neonatal Abstinence Syndrome (NAS) is a constellation of clinical symptoms of withdrawal that can affect neonates who had *in utero* exposure to licit or illicit substances. The central nervous system, autonomic nervous systems and gastrointestinal system are most notably dysregulated neonates affected with NAS[42]. Clinical manifestations of NAS include symptoms such as poor sucking, watery stools, tremors, irritability, tachypnea, and interrupted sleep pattern.

The accelerated increase of OUD in pregnant women in the last decades in combination with the growing opioid epidemic have led to a staggering increase in Neonatal Abstinence Syndrome[43]. In 2016, the US Food and Drug Administration introduced the term Neonatal Opioid Withdrawal Syndrome which is used to identify infants with withdrawal secondary to *in utero* opioid exposure specifically[44,45]. NOWS is considered a subset of NAS. Neonates who develop NOWS can have an array of medical complications such as poor feeding, inability to gain weight and failure to thrive as a consequence of withdrawal. In addition, infants with withdrawal are at a higher risk for long term effects such as poor neurodevelopmental, behavioral and educational outcomes[46–48]. Clinicians who are caring for neonates at risk for NOWS should complete a comprehensive medical screening of the infant's mother medical history, social habits and medication history to identify any illicit drug use and potential exposures. The aforementioned assessment serves to identify neonates at risk, provide counseling to families and to allocate appropriate treatment and resources.

The gold standard test for neonatal drug exposure is toxicology evaluation of the newborn's first stool, the meconium. This non-invasive and readily available sample can be tested for a variety of substances and has the ability to evaluate drug exposure throughout a longer window of detection. Symptom onset can occur as early as twenty-four hours of life to seventy-two hours of life. Onset of symptoms can also be stratified by substance as summarized by Kocherlakota[42], where heroin-associated NOWS presents with the shortest onset at twenty-four hours and methadone-associated NOWS can have the most prolonged onset, at seventy-two hours of life. It is important to note that a significant percentage of neonates with in utero opioid exposure will present symptoms by five days of life[42].

The modified Finnegan scoring is a comprehensive scale used by many U.S. physicians to assess the severity of

neonatal withdrawal. Finnegan scores also allow for continuous evaluation of worsening symptoms and management, as infants are assessed every four hours. A numerical scoring for the neonates' symptoms is given for disturbances in three main categories: central nervous system, metabolic/vasomotor and gastrointestinal. Traditional scoring systems, like the Finnegan Score, have been generally used in term infants only, as premature infants' clinical symptomatology differs from term neonates. Withdrawal symptoms in preterm neonates can be expressed as less severe than term infants presumably due to their premature central nervous system, immature opiate receptors and a shorter *in utero* exposure[49]. Recent studies by Amiri and Nair[50] in 2022, have shown that newer NAS scoring modalities such as eat, sleep, console (ESC) may offer an appropriate scoring system for premature infants with NAS. Validation of these newer modalities for the premature neonate population is still needed.

Management of NOWS can be stratified into non-pharmacologic and pharmacologic treatment. Non-pharmacologic management is based on supportive care techniques that aim to provide a quiet, low stimuli environment. Supportive care includes a quiet, dimly lit environment, soft music, swaddling, rocking or swinging, skin to skin with parents and the use of a pacifier. Parental involvement in supportive care techniques is highly encouraged to promote infant's wellbeing. Pharmacologic treatment is indicated when supportive care measures have been maximized and Finnegan scores remain consistently elevated. Neonates who meet criteria for pharmacological treatment should begin medication as soon as possible to prevent increase in morbidity. Oral morphine has been historically the first line pharmacological treatment for withdrawal due to its short half-life and ease of titration and weaning. Discussions regarding the use of other medications for withdrawal treatment has gained popularity, particularly methadone and buprenorphine. A recent study published by Davis et al[51] in 2018 compared the safety and efficacy of methadone versus morphine for the treatment of NAS. Davis et al randomized control trial demonstrated that the use of methadone led to a reduced hospital length of stay and reduced length of treatment. Furthermore, buprenorphine use has been studied by Kraft et al[56]in a single center clinical trial and buprenorphine use for treatment of NOWS gathered promising results in comparison to morphine. Furthermore, a meta-analysis conducted by Zedler et al[57] in 2016 which included randomized control trials and cohort studies showed moderately strong evidence that infants of mothers who were treated with buprenorphine had a lower risk of preterm birth and a greater birth weight. More research is needed to address the use of methadone and buprenorphine as pharmacologic interventions for NOWS.

Conclusion:

OUD in pregnancy is an increasingly frequent challenge to both maternal and fetal well-being. Opioid related overdose is now the leading cause of maternal mortality in several states, with the majority of these deaths deemed preventable[1]. Use of MAT in pregnancy, whether with Methadone or Buprenorphine has been shown to reduce the risk of relapse and overdose in this patient population. It has also been linked to improved pregnancy outcomes with adherence to MAT showing a reduction in preterm births.

Recognition of the significant barriers to care these patients face is also warranted. Many pregnant patients with OUD are reluctant to seek care due to mandatory state referrals to child welfare services, with their children increasingly being placed into foster care[52]. Parental substance use now accounts for the majority of infant foster care placements, with marked racial disparity. Recent studies have shown that black pregnant women are much more likely to have their children placed in the welfare system, and are much less likely than white parents to be reunified[53].

Even when patients with SUD seek care, they face significant bias and stigma from health care professionals. Many providers believe that utilizing MAT is just "trading one drug for another"[54], despite strong evidence to the contrary. The ultimate goal of MAT should be considered as stabilizing the patient from a chronic debilitating condition, reducing the risk of relapse and deadly overdose and allowing the patient to regain a foothold towards lasting recovery. The stability provided by MAT, along with access to addiction counseling, mental and medical health services allows patients to obtain gainful employment, family unification, reintegrate into society and live to their full potential[55]. Improved access to MAT should be prioritized by obstetric and addiction medicine providers.

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