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EDITORIAL



How does a clinician approach the pharmacological management of opioid use disorders in pregnant women and pregnant people?

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1. The public health challenge

The United States remains in the midst of at least its third opioid overdose epidemic. Within this current overdose epidemic are several distinct waves beginning with prescription opioid deaths in the late 1990s followed heroin overdose deaths in 2010 and since 2013 an ever-rising rate in fatal overdoses involving synthetic opioids (e.g. fentanyl). While opioid use disorder rates have been stable over time, dying from opioids greatly increased with a 25.9% increase in opioid-related overdose deaths from April 2020 to April 2021, representing 56,064 and 75,673 deaths, respectively [1]. In 2017, economists estimated the economic burden of opioid use disorder (OUD) and fatal opioid overdose on the USA was \$1.02 trillion [2]. Like other substance use patterns, rates of opioid use among pregnant women and pregnant people have paralleled the non-pregnant population. From 2000 to 2017, the national rates of maternal OUD at delivery increased from 1.1 to 8.2 per 1000 delivery hospitalizations [3,4]. Likewise, the diagnoses of opioid withdrawal following prenatal opioid exposure, also known as neonatal abstinence syndrome or neonatal opioid withdrawal syndrome (NAS/NOWS), increased from 1.2 to 7.3 per 1000 birth hospitalizations from 2000 to 2017 [4,5].

The harms of untreated OUD during pregnancy compared with those without OUD included increased odds of maternal cardiac arrest, preterm labor, placental abruption, premature rupture of membranes, cesarean delivery and death during hospitalization. For the neonates born to pregnant women and pregnant people with untreated OUD compared to neonates born to birthing people without OUD, they were at increased odds of intrauterine growth restriction, oligohydramnios, and stillbirth [6]. Risk factors for adverse neonatal outcomes may be related to contextual factors of living in marginalized contexts such as inadequate nutrition, stress, and trauma, rather than to the substance of prenatal exposure [6]. Complications in the prenatally opioid-exposed neonate may be partially due to fetal asphyxia which may occur during overdose or withdrawal [7]. Further, neonates diagnosed with NAS/NOWS may have longer and more complicated hospital stays than non-prenatally

opioid exposed neonates [6]. Treatments such as methadone or buprenorphine to treat OUD (known as medication to treat OUD; MOUD) during pregnancy significantly improved birthweight and reduced growth restriction in prenatally exposed neonates compared to neonates born to patients with untreated OUD during pregnancy [8].

2. Not just opioids: co-occurring issues

Most people have an OUD long before they become pregnant. It is also common for the OUD to occur with use of tobacco/vaping, cannabis, stimulant use or other use or use disorders. People who present to treatment for OUD during pregnancy often report a lifetime of traumatic events (e.g. physical, sexual, and emotional abuse) in childhood and adulthood [9]. They may have co-occurring depression, anxiety, posttraumatic stress disorder, bipolar disorder, or personality disorders [10]. Further, pregnant people with OUD often present with multiple medical and dental issues, poor nutrition, dehydration and are logically fearful of medical care due to the possibility of being reported to legal authorities or child protective services. Thus, the care provider must earn the patient's trust in order to provide optimal care and reduce the harm that ignoring these issues may have on initial birth outcomes and later child development [10].

A critical question is what are the considerations and treatment approaches which can reduce harm and promote healthy outcomes for both the patient with OUD during all trimesters of pregnancy and the first 12 weeks postpartum, the fourth trimester, and their child.

3. Shared decision-making approach with patients

Shared decision-making and decision aids may help facilitate patient-prescriber discussions of medication treatment options and patients abilities to make informed treatment choices. Within these shared decision-making conversations and aids, the following information regarding medication may be helpful (refer Table 1) [11].

Table 1. Medication shared decision-making considerations. The table provides a summary of topic domains and issues within each domain to consider.

Domain	Consideration Points
Additional Resources	A number of resources are available to help support providers and staff in developing and implementing shared decision making. Some of these resources can be found in the following websites: • https://www.ahrq.gov/health-literacy/professional-training/shared-decision/tool/resource-8.html, International Patient Decision Aid Standards (IPDAS) http://www.ipdas.ohri.ca/ • https://prcp.psychiatryonline.org/doi/full/10.1176/appi.prcp.20180004 for an example of shared decision making with pregnant patients receiving MOUD.
Ensure administrative, technical, and training supports are in place to establish shared decision making in clinics	• Every staff member who interacts with pregnant patients needs to be trained to understand the shared decision-making elements and their role in the shared decision-making process. • Successfully implementing shared decision making requires a coordinated plan and leadership buy-in. • A number of key activities to consider as part of the coordinated planning process include: (1) Obtain leadership support for any staff time for development, training creation of protocols and decision-making aids and the overall concept of shared decision-making improving care quality and patient outcomes. (2) Develop an implementation team and define roles and responsibilities. (3) Select a shared decision-making approach that is tailored to the patients and practice setting. (4) Provide training and ongoing support to all staff on their roles in the process. (5) Create a shared space on-line or physical space for a library of evidence-based educational resources and decision aids. (6) Create a physical setting for shared decision making. (7) Streamline the shared decision-making workflow processes into day-to-day operations and build in discussions and troubleshooting of the issues into regular staff meetings. (8) Start small, evaluate the process by asking all stakeholders and patients about the positive and negative aspects of how shared decision-making is being implemented, revise as needed and then consider increasing its scale and reevaluating it again.
Screening	• Normalize by noting that all pregnant patients are asked questions about substance use and also provide information about what happens to the screening information, especially if the patient endorses using substances.
Assessment	• An assessment is the beginning of a therapeutic relationship. • Should be a fluid process throughout the course of treatment – given changes in physical and psychological functioning as a result of treatment, it is critical to assess the response to medication and other aspects of care periodically throughout pregnancy and the postpartum period. • Medical history, nutrition, psychiatric status, social functioning, interpersonal safety, home situation, Obstetrical history, substance use treatment objectives, OUD treatment history and preferences and current medications.
Medication Considerations	• Previous stabilization • Response to methadone or buprenorphine • Past refusal of medication type • Preference and reasons for preference • Proximity, affordability, transportation, payment options • Medication interactions
Induction in any Trimester	• Current opioid use (route, type, amount) and period of reduction or ability to be fully opioid-free. • Setting for induction (hospital, office, home) • Starting dose and rapidity of induction • Safe storage of medication • Naloxone overdose kit and training in how to use it
Stabilization	• Regular review of withdrawal and oversedation • Dose adjustments that include split or thrice daily dosing • Increased total daily dose over advancing pregnancy • Develop a birth plan – meet with anesthesia and tour L&D and postpartum, pediatrics, neonatology; talk about benefits of breastfeeding and neonatal withdrawal and how it will be assessed and what parents can do to help.

(Continued)

Table 1. (Continued).

Domain	Consideration Points
Pain Management	• Continue methadone or buprenorphine without dosing interruption. • Assess pain and provide epidural • Avoid partial agonist/antagonists • Give short acting opioids for pain control if needed • Provide smoking cessation products to reduce pain increased due to tobacco withdrawal.
Fourth Trimester	• Screen for post-partum depression and respond if endorsed. • Keep regular contact with patient – every two weeks • Ensure post-partum follow-up • Discuss contraception plans and enact them- make sure they do not interfere with breastfeeding. • Review dose and adjust if over-sedated, ensure plan for continuation on medication using shared decision making.

4. Medication to treat opioid use disorder versus detoxification

Methadone and buprenorphine are endorsed by the American College of Obstetricians and Gynecologists and a wide variety of American and international health authorities [12]. MOUD is the optimal treatment for OUD during pregnancy. The goals of induction are the same for all patients, pregnant or not: cease withdrawal and then prevent future opioid misuse. For pregnant patients, MOUD reduces large variations in opioid blood levels that come with using short-acting opioids like heroin. These fluctuations resulting in extremes of high opioid levels and withdrawals are hypothesized to increase neonatal risks. Access to both MOUD and prenatal care improves maternal and neonatal outcomes [13]. While MOUD does not cure OUD, it can be essential to setting the occasion for sustained remission of OUD.

Results of a systematic review demonstrate that the MOUD is far more effective than detoxification (e.g. low completion rates and high rates of return to illicit substance use). While fetal loss was similarly low among women who did (1.2%) and did not (2.0%), undergo detoxification, the risk of NAS/NOWS was not mitigated by discontinuation of agonist medication [14]. Further, detoxification should also be avoided because of concerns of exposure to withdrawal, return to potentially unsafe substance use and associated infection risk for the pregnant person and their fetus (HIV, Hepatitis C etc.).

While detoxification is not recommended, many pregnant people receive detoxification because of provider preference or they are not able to access MOUD due to lack of availability, difficulties with transportation or childcare, or concerns about child welfare consequences if their neonate tests positive for their prescribed medication or has opioid withdrawal.

Methadone, buprenorphine alone and more recently recommended, buprenorphine in combination with naloxone are now the primary options to treat opioid use disorder during pregnancy [12]. Methadone is a full mu opioid agonist with a long half-life, that block opioid withdrawal and craving. Buprenorphine is a partial mu opioid agonist and kappa antagonist. Its pharmacology yields a ceiling effect for respiratory depression and improved adverse effect profile when compared with full agonists. Buprenorphine combined with the opioid antagonist naloxone is advantageous to reduce misuse and diversion and has less NAS/

NOWS severity. Individualized dosing for both methadone and buprenorphine including split or thrice-daily dosing may be needed in addition to total daily dose increases with advancing gestation. In terms of comparing the efficacy and safety of methadone and buprenorphine, for the birthing person outcomes are similar and for the child there is moderately strong evidence supporting less preterm birth, greater birth weight and larger head circumference with buprenorphine compared with methadone [15]. When selecting a MOUD, the patient's past response to medication is important, as is their ability to afford it, obtain it and adhere to the structure related to the medication. A study comparing methadone and buprenorphine found that over 66% of the time buprenorphine was the cost-effective strategy relative to methadone or detoxification to treat OUD during pregnancy [16]. For patients who have not previously taken MOUD, it is easier to start buprenorphine and transition to methadone than the reverse. Naltrexone an opioid antagonist blocks the effects of opioid agonists and is currently being examined for relative maternal, fetal and child safety and efficacy for treating opioid use disorder during pregnancy [17]. Interest in naltrexone as a treatment is based on its blockade of opioid agonist euphoric effects, its lack of misuse potential, lack of tolerance development and lack of producing NAS/NOWS in the neonate. However, it is not without concerning potential drawbacks, including the difficulty surrounding medication induction during pregnancy [18].

5. Continuing care in the fourth trimester and beyond

Adequate pain management, breastfeeding, keeping birthing parent and neonate together and involving the parent as part of the care team can all improve NAS/NOWS and outcomes [19]. The US has alarmingly high rates of maternal mortality. Racial and ethnic disparities that exist throughout the pregnancy-postpartum continuum, must be addressed as well as the under-reported issue of maternal self-harm [20]. Health care delivery failures, including inadequate risk assessment, care coordination, and communication, are drivers of maternal health disparities and self-harm. Suicide and overdose are leading but under-recognized causes of death among pregnant and postpartum people. Many of the same steps to

improve quality of perinatal care can help to reduce health disparities and address the essential role of mental health in maternal well-being [21]. Successful partnerships between obstetricians, pediatricians, and specialists in addiction medicine can improve access to MOUD while ensuring patient engagement in care throughout the first year post-partum [22].

6. Expert opinion

With the advent of more designer forms of fentanyl and methamphetamine, the survival benefit of methadone and buprenorphine are even more compelling than ever before. Ensuring pregnant people has access to these medications is especially important because drug overdose is a leading cause of maternal death in the postpartum period. Further, the field is at a critical juncture where new induction protocols rapidly need to be studied within a large network to quickly determine when and how to use micro or macro buprenorphine induction protocols and how safely provide rapid methadone inductions. Induction protocols likely work for all patients, regardless of pregnancy. The COVID pandemic provided a natural experiment to loosen the strong behavioral structure of methadone access. An important next step would be to allow split or multiple daily dosing of perinatal patients as standard care practice and to allow primary care prescribing of methadone, with dispensing from hospital and community pharmacies [23]. Not all OUD treatment programs for pregnant and parenting people are equally effective. Compassionate treatment requires individualized treatment plans and regular progress review of medication and behavioral health during and years after pregnancy. Further, children need to be considered in treatment and given opportunities for early intervention to promote healthy life development. Research does not indicate that Child Protective Service reporting and Child Abuse/Neglect policies lead to reductions in use during pregnancy or to improved birth outcomes [24]. Thus, now is the time to change our outdated research questions such as: what proportion of pregnant people drink alcohol and use drugs, what proportion of children are identified as being prenatally exposed to opioids or other substances and what are the short- and long-term effects of pregnant people drinking alcohol and use drugs (including opioids) on maternal and neonatal health? and consider future-forward questions such as: To what extent do the policies we enact actually improve birthing parent, fetus, neonate and child health, safety and well-being and to what extent do the policies we enact yield equitable health, safety and well-being outcomes for the birthing parent, fetus, neonate and child?

Note: This publication acknowledges that not every person with the capacity for pregnancy identifies as a woman. It is important for health care professionals to recognize the aim to be inclusive and respect each individual's gender identity, expression, and experience, and be helpful to all who need care during the perinatal time. Gender-inclusive language (person/people/they/them/patient) as well as woman/women in some cases, depending on the context and literature being cited. Use of such language acknowledges the long history of gender discrimination focused on women and the specialized health care documents and

research that has been published about women. Further, the use of inclusive language aims to model competency and is not aimed to undermine or eliminate the primacy of women in birth. Using gender-neutral language in no way forces people to eliminate women from their vocabulary. Rather, it sets a standard for professionals to serve a wide range of people with birthing capacity.

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Declaration of interest

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