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# The MATernaL and Infant NetworK to Understand Outcomes Associated with Treatment of Opioid Use Disorder During Pregnancy (MAT-LINK): Surveillance Opportunity

**Emmy L. Tran, PharmD, MPH**[1,2], **Shin Y. Kim, MPH**[2], **Lucinda J. England, MD, MSPH**[2], **Caitlin Green, MPH**[2], **Elizabeth P. Dang, MPH**[2], **Cheryl S. Broussard, PhD**[2], **Nicole Fehrenbach, MPP**[2], **Amy Hudson, MA, LNHA, PMP**[2], **Tineka Yowe-Conley, MPA**[2], **Suzanne M. Gilboa, PhD**[2], **Dana Meaney-Delman, MD, MPH**[2]

[1]Eag1e Global Scientific LLC, san Antonio, Texas, USA

[2]Division of Birth Defects and Infant Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

## Abstract

Pregnant women with opioid use disorder (OUD) are at risk of overdose, infectious diseases, and inadequate prenatal care. Additional risks include adverse pregnancy and infant outcomes, such as preterm birth and neonatal abstinence syndrome. Management and treatment of OUD during pregnancy are associated with improved maternal and infant outcomes. Professional organizations, including the American College of Obstetricians and Gynecologists, recommend offering opioid agonist pharmacotherapy (*i.e.*, methadone or buprenorphine) combined with behavioral therapy as standard treatment for pregnant women with OUD. Other medications and herbal supplements have also been used by pregnant women for OUD. Determining which OUD treatments optimize maternal and infant outcomes is challenging given the host of potential factors that affect these outcomes. The Centers for Disease Control and Prevention initiated the MATernaL and Infant NetworK to Understand Outcomes Associated with Treatment of Opioid Use Disorder during Pregnancy (MAT-LINK) to monitor more than 2000 mothers and their infants, using data collected from geographically diverse clinical sites. Information learned from MAT-LINK will inform the future management and treatment of pregnant women with OUD.

### Keywords

opioid use disorder; substance use disorder; pregnancy; surveillance; outcomes

Address correspondence to: Emmy L. Tran, PharmD, MPH, Division of Birth Defects and Infant Disorders National Center on Birth Defects and Developmental Disabilities Centers for Disease Control and Prevention 4770 Buford Highway, NE MS S106-3 Atlanta, GA 30341 USA, nhu4@cdc.gov.

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## Background

PREGNANT WOMEN WITH opioid use disorder (OUD) face many challenges. OUD poses risks to the mother, such as fatal and nonfatal overdose, infectious diseases, or inadequate prenatal care, and risks for adverse pregnancy and infant outcomes, such as preterm birth and neonatal abstinence syndrome (NAS).[1,2] Between 1999 and 2014, the diagnosis of OUD (also referred to as opioid addiction or opioid dependence) quadrupled from 1.5 to 6.5 per 1000 delivery hospitalizations.[3] During the period 2005–2014, the National Survey on Drug Use and Health (NSDUH) reported that 5.1 % of pregnant women in the United States had used opioids for nonmedical purposes in the past year, and almost 90% of these women reported using at least one other substance, most commonly alcohol (51 %), cigarettes (42%), marijuana (35%), or tranquilizers and sedatives (24%).[4] The combined effects of prenatal substance and medication use, particularly combinations of nervous system depressants and/or known teratogens, such as alcohol,[5,6] may increase maternal and infant adverse outcomes.[7,8]

Treatment of OUD with opioid agonists (*i.e.*, methadone or buprenorphine) combined with behavioral therapy reduces the misuse of opioids, prevents withdrawal symptoms, decreases the risk of fatal and nonfatal overdose, and is associated with overall improved maternal and infant outcomes.[1,2] The current standard of opioid agonist OUD treatment during pregnancy was endorsed in 2015 by the American Society of Addiction Medicine (ASAM); in 2017 by the American College of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics (AAP), and jointly by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, ACOG, AAP, the Society for Maternal-Fetal Medicine (SMFM), the Centers Disease Control and Prevention (CDC), and the March of Dimes Foundation; in 2018 by the Substance Abuse and Mental Health Services Administration (SAMHSA); and in 2019 jointly by ASAM, ACOG, and SMFM.[1,2,9–12] Although not routinely used during pregnancy, some providers offer naltrexone and medically supervised withdrawal. Additionally, medications and herbal supplements (*e.g.*, clonidine[13,14] or loperamide[14,15] and kratom,[16–19] respectively) are sometimes used in clinical management protocols or as self-Yeatment for OUD.

Questions remain about how to best manage and treat pregnant women with OUD to optimize and infant health outcomes. In early 2020, the National Center on Birth Defects and Developmental Disabilities at the CDC initiated the MATernaL and Infant Network to Understand Outcomes Associated with Treatment of Opioid Use Disorder during Pregnancy (MAT-LINK) to assess maternal and infant outcomes. MAT-LINK will capture data on maternal and infant outcomes across geographically diverse clinical sites from over 2000 mother–infant pairs for up to 2 years after delivery. Information learned from MAT-LINK will inform the future management and treatment of pregnant women with OUD. The purpose of this report is to describe medications and herbal supplements used by pregnant women for OUD, provide information on associated pregnancy and infant outcomes, and discuss how MAT-LINK can address gaps in knowledge about the management and treatment of OUD during pregnancy.

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## Medications and Herbal Supplements Used by Pregnant Women for OUD

We searched PubMed with the following medical subject heading terms: “substance-related disorders” and “pregnancy” and reviewed recent publications[20] to identify published articles containing prevalence estimates of OUD management practices among pregnant women and pregnancy and infant outcomes. A total of six medications or herbal supplements were identified to be used by pregnant women for OUD: methadone, buprenorphine, naltrexone, clonidine, loperamide, and kratom. Medications and herbal supplements both have potential for misuse, as shown in Figure 1. These medications and herbal supplements were those most commonly encountered, but they are not comprehensive of all medications potentially used for OUD during pregnancy.

**Opioid agonist treatment: methadone and buprenorphine—**Methadone, an opioid agonist, was approved by the Food and Drug Administration (FDA) in 1964 for maintenance treatment of OUD in conjunction with appropriate social and medical services in nonpregnant adults.[21] Women, including pregnant women, who use methadone for OUD treatment are required to attend an opioid treatment program daily to receive supervised maintenance treatment. Beginning in the 1970s, methadone has been the standard of care for OUD treatment during pregnancy, and in 1998, methadone maintenance treatment for pregnant women with OUD was recommended by the National Institutes of Health.[22,23] Treatment has been associated with improved prenatal care and decreased risk of fetal stress and stillbirth associated with opioid withdrawal.[24]

Buprenorphine, a partial opioid agonist, was approved in 2002 for nonpregnant adults and recommended as an option for OUD treatment during pregnancy in 2015.[1,2,9,10,12,25] Buprenorphine is the only opioid agonist that can be obtained from a qualified provider with a Drug Addiction Treatment Act of 2000 (DATA 2000) waiver, which allows for OUD treatment with FDA-approved controlled substances to be prescribed outside of opioid treatment programs.[2]

Both methadone and buprenorphine are long-acting prescription medications that can also be prescribed for pain management and are designated by the Drug Enforcement Administration as controlled substances.[26] A combination product of buprenorphine with naloxone (brand name Suboxone) is available as an OUD treatment option, but not currently recommended for use during pregnancy. The addition of naloxone, an opioid antagonist, to the combination pill discourages misuse of buprenorphine intravenousl and is recommended for nonpregnant adults with OUD.[9] Although this combination product is not FDA-approved or recommended for use during pregnancy due to limited information on the safety of naloxone during pregnancy, this drug has been used in clinical practice for pregnant women, often in the context of a nonpregnant individual on maintenance treatment who becomes pregnant.[1,2,9,12]

ACOG and other professional organizations recommend that opioid agonists be offered to all pregnant women with OUD, and the choice of methadone or buprenorphine during pregnancy should be individualized based on patient-specific characteristics, such as patient preference, treatment regimen before pregnancy, product availability, cost or insurance

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coverage, severity of disease, comorbidities, and potential drug–drug interactions with maternal medications.[1,2,9,12]

National population-based prevalence estimates of methadone or buprenorphine treatment among pregnant women with OUD and stratified by medication type are not available. Current prevalence estimates for treatment among pregnant women with OUD range from 8% to 80% for methadone and from 16% to 75% for buprenorphine; however, these studies are limited to clai.ms data,[27,28] medical centers,[29–31] or individual clinics,[32–34] and estimates vary widely by time period, geographic location, urbanization level, treatment setting, and sampling methods.

While SAMHSA's Treatment Episode Data Set provides prevalence estimates of pregnant women in the United States treated with opioid agonists for programs that receive public funding and includes data from outpatient, intensive outpatient, and residential treatment programs, this dataset does not specify which medications are used nor does it include office-based buprenorphine maintenance therapy outside of opioid treatment programs.

In a recent report, receipt of opioid agonists among pregnant women with OUD remained static from 1996 to 2004, at about 50%.[35] Similarly, data from the 2002 to 2006 NSDUH reported that among women who used drugs, pregnant women were almost two times more likely to need treatment (defined as self-reported need for substance use disorder [SUD] treatment in the last 12 months or meeting criteria for substance dependence) than nonpregnant women. However, data from the 2002 to 2014 NSDUH indicate that pregnancy status does not increase rates of treatment (defined as self-reported treatment in the last 12 months received at drug or alcohol rehabilitation facilities, hospitals, mental health centers, emergency rooms, private doctor's offices, prisons/jails, or self-help groups) among women who needed treatment,[36–38] and data from the 2002 to 2006 NSDUH indicated that only about 9% of pregnant women who needed treatment for SUDs received treatment.[36] Reports did not provide separate estimates of methadone and buprenorphine use; however, these data indicate a gap in treatment receipt among pregnant women with SUDs.

Methadone and buprenorphine comparison: pregnancy and infant outcomes. Professional organizations recommend offering individualized opioid agonist pharmacotherapy treatment plans (*i.e.*, methadone or buprenorphine) combined with behavioral therapy as standard treatment for pregnant women with OUD.[1,2] Use of opioid agonists during pregnancy has been associated with the risk of adverse pregnancy and infant outcomes, such as preterm birth[39] and NAS,[40] which has been described as a constellation of signs and symptoms related to withdrawal that neonates may experience after birth if prenatally exposed to psychotropic substances (*e.g.*, opioids). However, NAS is a treatable condition, and OUD treatment with opioid agonists is associated with improved maternal and pregnancy outcomes (*e.g.*, increased prenatal care, reduced risk of infectious diseases related to intravenous drug use, and decreased risk of fetal loss associated with untreated OUD).[1,12,41–45]

Patient-specific characteristics should be assessed when considering the risks and benefits of OUD treatment during pregnancy. Two systematic reviews compared pregnancy outcomes

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between these opioid agonists. However, more data are needed to determine the optimal treatment regimens for each medication during pregnancy.

Zedler et al.[39] reported that women treated with buprenorphine experienced a lower rate of preterm birth compared with those treated with methadone. Among the included studies, none were sufficiently powered to detect differences in fetal loss or birth defect rates, and there was insufficient evidence to evaluate differences in intrauterine growth restriction, small for gestational age, or maternal adverse events. Additionally, none of the studies assessed rates of maternal relapse. No difference was detected in effect estimates for any outcome between use of the combination product of buprenorphine and naloxone and use of buprenorphine monotherapy. Details, including onset and duration of OUD treatment and confounders such as the severity of OUD and concomitant prenatal substance use, were not captured in many studies, and statistical power was insufficient to detect differences in outcomes.[39]

A second systematic review of methadone and buprenorphine treatment of OUD in pregnancy by Bivin et al.[40] reported that buprenorphine was associated with shorter lengths of birth hospital stay for infants and decreased frequency or duration of NAS treatment when compared with methadone. However, buprenorphine was associated with decreased risk for concomitant illicit drug use, which could affect these measured outcomes. The evidence was insufficient to determine whether outcomes were affected by differences in OUD severity.[40]

## Other OUD Management Options: Naltrexone and Medically Supervised Withdrawal

**Naltrexone—**Naltrexone is a prescription opioid antagonist that was approved by the FDA in 1984 prevention of opioid dependence relapse in nonpregnant adults. Initiation of naltrexone is recommended after a 7–10-day opioid-free to prevent inadvertent induction of opioid withdrawal.[46] Due to the required opioid tapering and limited data on safety and efficacy, naltrexone is not recommended for pregnant women with OUD.[1,2,9,11,12] Studies assessing naltrexone use during pregnancy had only been conducted outside of North America, with most evaluating an implantable formulation not yet approved by the FDA for use in the United States.[47] At the time of this review, there are no published estimates available for the prevalence of naltrexone used among pregnant women in the United States for treatment of OUD. Two observational cohort studies recently published, which included pregnant women in the United States, are summarized below [48,49]

One small, retrospective cohort study[49] included six pregnant women with OUD who were with naltrexone compared with 13 women who were treated with buprenorphine. This small study demonstrated a significantly lower incidence of NAS and a significantly shorter length of birth hospital stay for infants in the naltrexone group. A larger, prospective cohort study[48] found that pregnant women who were treated with naltrexone up until delivery experienced no occurrence of relapse during the opioid tapering period before naltrexone initiation, no complications related to ineffective pain management at labor and delivery, and no cases of spontaneous abortion, stillbirth, or NAS. This study included women who were already on naltrexone before conception ($n$ = 11) and women who initiated naltrexone during pregnancy, either before 24 weeks' gestation ($n$=46) or after 24 weeks' gestation ($n$=64); all women adhered to behavioral health visits and prenatal care throughout pregnancy.

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More evidence is needed to confirm these findings, to determine the optimal timing of naltrexone initiation during pregnancy, and to directly compare safety and efficacy outcomes of naltrexone with other OUD treatments for pregnant women.

**Medically supervised withdrawal—**SAMHSA defines medically supervised withdrawal as using a medication in tapering doses to help a patient discontinue illicit or prescription medications.[1] This approach has also been referred to as detoxification; however, professional organizations, including SAMHSA and ASAM, have replaced this term to prevent misconceptions regarding the safety of OUD pharmacotherapy.[1,9]

According to a 2018 systematic review of outcomes associated with medically supervised withdrawal during pregnancy, 9 of 13 studies included pregnant women in the United States who had medically supervised withdrawal in inpatient settings. Most studies in the United States included in the review involved at least one tapering medication for medically supervised withdrawal, while only one study enrolled patients in a solely drug-free, residential treatment program. Treatment commonly involves the use of opioid agonists in tapering doses (as opposed to maintenance doses) or non-opioid medications, such as clonidine, while under the supervision of a health care provider to manage withdrawal symptoms.[50]

ACOG and other professional organizations do not recommend medically supervised withdrawal during pregnancy due to the risk of relapse and adverse pregnancy outcomes and state that it should only be an option if opioid agonist treatment is not acceptable to the patient or is unavailable.[1,2,12] However, based on the 2018 systematic review,[50] medically supervised withdrawal has increasingly been documented in recent years as a provided option for pregnant women with OUD to prevent NAS and associated health care costs. Completion and relapse rates vary, ranging from 9% to 100% for completion and 0%–100% for relapse. Insufficient evidence is available to determine maternal and neonatal outcomes beyond delivery. Thus, the relative safety and efficacy of medically supervised withdrawal during pregnancy have not yet been established, and the characteristics of pregnant women who may be the best candidates for this option are not known.

**Medically supervised withdrawal and self-treatment: other medications and herbal supplements.:** Other medications (*e.g.*, clonidine[13,14] and loperamide[14]) are not used as OUD maintenance treatment, but according to ASAM,[9] they are sometimes used as medication options for medically supervised withdrawal for nonpregnant adults. However, these medications are not FDA approved to treat opioid withdrawal and are not recommended by ACOG and other professional organizations for opioid withdrawal management during pregnancy.[1,2,9] Both clonidine and antidiarrheals, such as loperamide, have been used clinically for medically supervised withdrawal among pregnant women to manage symptoms of opioid withdrawal, including autonomic symptoms, such as hypertension, tachycardia, sweating, and diarrhea.[13,14] Women who do not receive clinician-supported OUD treatment may self-treat opioid withdrawal symptoms with over-the-counter (OTC) medications or herbal supplements. For example, misuse of loperamide, an OTC antidiarrheal, has recently been reported in an attempt to self-treat opioid withdrawal during pregnancy.[15] Kratom, an herbal supplement derived from tropical tree leaves native to

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Southeast Asia,[20] has been used by pregnant women in the United States who were opioid withdrawal symptoms.[16–19,51] No published prevalence estimates are currently available for these two nonprescription products among pregnant women with OUD in the United States.

## CDC's Surveillance System for OUD Management and Treatment During Pregnancy–MAT-LINK

As described above, many questions remain about the management and of OUD during pregnancy. In addition, little is known about long-term outcomes of women receiving OUD treatment during pregnancy and their off-spring. Longitudinal follow-up of women with OUD and their children is needed to fully understand maternal, infant, and childhood outcomes. The developmental trajectory of children whose mothers have OUD and those with *in utero* exposure to medications and herbal supplements used for OUD has not been systematically studied. Furthermore, the impact of polysubstance use, maternal comorbid conditions, and environmental and psychosocial factors will be important to consider in any analyses, although these may be difficult to disentangle as confounders.

To improve the understanding of outcomes associated with management and treatment of OUD during pregnancy, CDC initiated MAT-LINK in early 2020, a health outcomes surveillance network, which will collect maternal and offspring data among women managed and for OUD during pregnancy for up to 2 years after delivery. MAT-LINK objectives are (1) to compare maternal, infant, and child health outcomes across OUD management and treatment regimens to inform future clinical practice, (2) to examine the possible effects of exposure to multiple substances and other risk factors on maternal and infant outcomes, and (3) to develop a data platform and infrastructure to collect linked maternal and offspring data (Table 1).

MAT-LNK is an innovative surveillance system that will build the infrastructure to address many of the gaps in knowledge related to OUD management and treatment among pregnant women. Based on subject matter expert and partner input, MAT-LINK identified pertinent maternal, infant, and child data elements to capture (Table 2). Treatment groups will include women who are treated with pharmacologic therapy (*i.e.* methadone, buprenorphine with or without naloxone, and naltrexone), women receiving medically supervised withdrawal, or women receiving no treatment, with or without behavioral therapy.

Surveillance data will be obtained from medical, pharmacy, laboratory, administrative, and other records for both mother and child. Data elements will include maternal health history, pregnancy and postpartum outcomes, maternal and newborn delivery outcomes, and offspring measures of early childhood development. MAT-LINK will also collect data on social determinants of health and demographic factors (*e.g.*, zip code, insurance status, and race/ethnicity), prenatal exposure to infectious diseases (*e.g.*, viral hepatitis), OUD management and treatment (*e.g.*, timing of onset, duration, frequency, and intensity), use and misuse of other medications (*e.g.*, benzodiazepines, barbinrates, and loperamide), and recreational use of licit/illicit substances (*e.g.*, alcohol, tobacco, heroin, and kratom); herbal supplements may be captured in the context of recreational substance use, but otherwise will not be routinely collected. Details on outcomes related to maternal relapse rates, NAS, and infant developmental screening will also be captured. Additionally, MAT-LINK data

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may help to determine how the delivery of care for pregnant women with OUD is impacted during emergency responses, such as the coronavirus disease 2019 (COV11)-19) global pandemic.

Currently, four MAT-LINK clinical sites have the maternal-infant data linkages and data infrastructure to capture clinical data about pregnant women managed and treated OUD who during or after 2014. MAT-LINK will create a common data network among these clinical sites, which will inform future data and allow for collection of data in a standardized way other clinical networks. This network is expected to compile one of the largest datasets on this topic from multiple institutions with common data elements, which allows for robust analysis of clinical practices and outcomes and will inform future clinical guidelines for the management of OUD during pregnancy locally as well as nationally. Moreover, this network of four clinical sites has the potential to be expanded to other clinical networks treating women with OUD and to as a model system adaptable for other mother-baby exposures, treatments, and outcomes.

Pregnant women affected by OUD are an underserved population, and appropriate management and treatment are critical to prevent relapse, the spread of infectious diseases, and interruptions in prenatal care and to optimize pregnancy and infant outcomes.[1,2,36] Through partnerships with federal, clinical, and public health partners, MAT-LINK has established a surveillance infrastructure to collect critical data about pregnant women in treatment for OUD. Better understanding of maternal, infant, and child outcomes associated with OUD and OUD management and treatment will improve the ability to maximize the health and well-being of mothers with OUD and their children.

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Disclaimer

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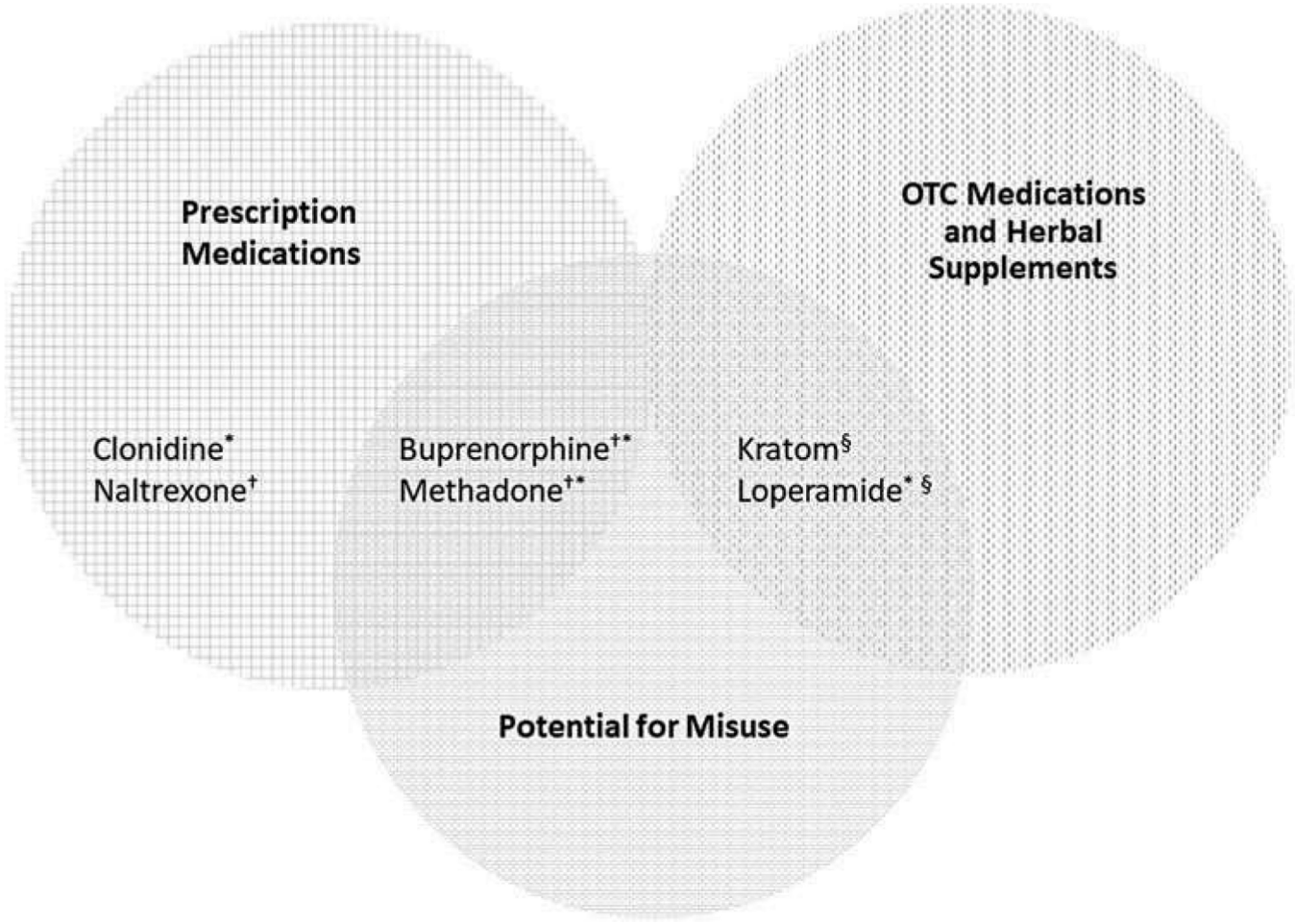


**FIG. 1.**

Medications or herbal supplements potentially used by pregnant women for OUD. *Medications potentially used for medically supervised withdrawal. †FDA approved for treatment of OUD. §OTC medications or herbal supplements potentially used to self-treat opioid withdrawal. FDA, Food and Drug Administration; OTC, over-the-counter; OUD, opioid use disorder. Color images are available online.

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**TABLE 1.**

KEY QUESTIONS TO BE ADDRESSED BY MAT-LINK

| |
|---|
| Clinical management of OUD in pregnancy |
| • What characteristics of pregnant women with OUD (*e.g.,* patterns of opioid use) predict which regimen is likely to be most effective before, during, and after pregnancy? |
| • How often and why do pregnant women switch OUD treatment regimens? |
| OUD treatment regimen and pregnancy and infant outcomes |
| Do the following outcomes differ across OUD treatment regimens? |
| • Risk of relapse and/or overdose among pregnant and postpartum women |
| • Pain management during labor and delivery |
| • Frequency of adverse birth outcomes (*e.g.,* preterm birth, pregnancy loss, and growth restriction) |
| • Risk of NAS and other infant outcomes |
| • Risk of developmental delay and other childhood outcomes |
| Other risk factors related to OUD treatment |
| Does the risk of pregnancy, infant, or child health outcomes differ depending on the presence of the following other factors? |
| • History of maternal physical or mental conditions |
| • Medications during pregnancy |
| • Specific polysubstance combinations used during pregnancy |
| • Development of NAS or NAS severity in infants |
| • Management of NAS with nonpharmacologic and/or pharmacologic regimens |
| • Receipt of postdischarge services and plans of safe care |

MAT-LINK, MATernaL and Infant Network to Understand Outcomes Associated with Treatment for Opioid Use Disorder during Pregnancy; NAS, neonatal abstinence syndrome; OUD, opioid use disorder.

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**TABLE 2.**

DATA ELEMENTS TO BE COLLECTED IN MAT-LINK

| Category | Variables |
|---|---|
| Maternal health history | • Demographic information<br>• Social determinants of health (*e.g.,* education, incarceration status, insurance status, and zip code)<br>• Prepregnancy height and weight<br>• Pre-existing conditions<br>∘ Psychosocial history<br>∘ Substance use disorders<br>∘ Mental health conditions<br>∘ Other chronic conditions |
| During and after current pregnancy | • Prenatal visits<br>•Pregnancy weight<br>• Obstetric history<br>• Pregnancy-related infectious and noninfectious conditions<br>• OUD treatment and other medications—including timing, dose, duration, and frequency when available<br>∘ Opioid use before OUD treatment initiation<br>∘ OUD pharmacologic treatment (methadone, buprenorphine ± naloxone, naltrexone, and other site-specific options)<br>∘ Medically supervised withdrawal ± medications<br>∘ Psychosocial/behavioral therapy o Opioid-related return to use<br>∘ Overdose (opioid and nonopioid)<br>• Maternal prenatal and postdelivery substance exposure test results<br>• Recreational substance use—including timing, dose, duration, and frequency when available<br>∘ Alcohol<br>∘ CBD oil (*e.g.,* vaped or ingested)<br>∘ Cigarettes/cigarillos<br>∘ Cocaine<br>∘ Hallucinogens (*e.g.,* LSD, PCP, and ecstasy)<br>∘ Inhalants (*e.g.,* glue, nitrous oxide, and felt tips)<br>∘ Kratom<br>∘ Marijuana (*e.g.,* blunts, cannabinoids, hashish, and THC)<br>∘ Methamphetamine<br>∘ Other tobacco substances (*e.g.,* vaping [e-cigarettes with nicotine], cigars, and smokeless tobacco [*e.g.,* snus, snuff, chew, and hookah])<br>• Method of contraception at postpartum follow-up<br>• Emergency department visits and nondelivery hospitalizations<br>• Maternal death |
| Delivery (maternal) hospitalization | • Pregnancy outcome<br>• Plurality<br>• Delivery complications, location, and type<br>• Medications administered during labor and delivery<br>• Discharge destination and length of hospital stay |
| Birth (neonatal) hospitalization | • Infant sex<br>• Measurements at birth or first measurement<br>• Neonatal resuscitation measures in the delivery room<br>• Newborn screening (*e.g.,* blood spot testing, congenital heart disease, and hearing loss)<br>• Newborn substance exposure test results<br>• Newborn conditions, including the following:<br>∘ Anemia<br>∘ Asphyxia<br>∘ ECMO, number of days on ECMO<br>∘ Hemolytic disease |

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| Category | Variables |
|---|---|
| | ◦ Interventricular hemorrhage<br>◦ Intrauterine growth restriction/small for gestational age<br>◦ Hyperbilirubinemia/jaundice<br>◦ Necrotizing enterocolitis<br>◦ Oxygen administered<br>◦ PDA<br>◦ Major congenital anomaly/birth defects<br>◦ Sepsis<br>◦ Vertical transmission of infectious diseases<br>• NAS<br>◦ NAS protocol<br>◦ Newborn signs and symptoms related to NAS,[a] including the following:<br>■ Autonomic dysfunction (*e.g.,* sneezing, nasal congestion, yawning, fever, and cutaneous mottling)<br>■ Diarrhea or loose stools<br>■ Feeding problems (*e.g.,* vomiting and poor feeding)<br>■ Hypertonia<br>■ Hyperactive Moro reflex<br>■ Irritability (*e.g.,* continuous, excessive, or high-pitched cry and poor sleep)<br>■ Myoclonus<br>■ Respiratory distress/symptoms<br>■ Seizures<br>■ Tremors<br>• Pharmacologic newborn management, including timing, dose, duration, and frequency<br>• Nonpharmacologic newborn management<br>◦ Feeding method (*e.g.,* breastfeeding or formula feeding)<br>◦ Rooming-in<br>• Hospitalization location(s) and length of stay<br>• NICU admission<br>• Newborn death before discharge<br>• Discharge weight, destination, and newborn living situation<br>• Discharge planning (*e.g.,* plan of safe care, child protective services referral, and pediatrician identified for follow-up)<br>• Readmission or emergency room visit after birth hospitalization within 28 days related to NAS, treatment given, and length of stay |
| Child health history | • Primary care provider visits<br>◦ Primary reason for visit<br>◦ Growth measurements<br>◦ Developmental and behavioral surveillance and results from screening instruments<br>• Referral to specialists and receipt of services (*e.g.,* WIC, Early Head Start, and Early Intervention [Part C])<br>• All diagnoses and medications<br>• Laboratories (genetic, separate from newborn screen; lead; and infectious diseases)<br>• Dates of hospitalization, emergency room or urgent care visits, and surgeries<br>• Child death |

[a]Signs and symptoms of NAS will be site specific and depend on the NAS protocols used at each site.

CBD, cannabinoid; ECMO, extracorporeal membrane oxygenation; ISD, lysergic acid diethylamide; PCP, phencyclidine; PDA, patent ductus artaiosus; THC, tetrahydrocannabinol; WIC, The Special Supplemental Nutrition Program for Women, Infants, and Children.

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