

**MEDICATIONS USE AMONG PREGNANT WOMEN****Maha Abdulameer Oudah<sup>1</sup> and Alhan Hussien Abod\*<sup>2</sup>**<sup>1</sup>Ministry of Health, Baghdad, Iraq.<sup>2</sup>Ministry of Health - Baghdad Medical office, Al-Karkh, Al Ameel Sector, Health Center Associations, Baghdad, Iraq.Article Received on  
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Iraq.**ABSTRACT**

Medications use in pregnancy has escalated dramatically in recent years, paralleling the epidemic observed in the general population. To combat the medications epidemic, all health care providers need to take an active role. Pregnancy provides an important opportunity to identify and treat women with substance use disorders. Substance use disorders affect women across all racial and ethnic groups and all socioeconomic groups and affect women in rural, urban, and suburban populations. Therefore, it is essential that screening be universal. Screening for substance use should be a part of comprehensive obstetric

care and should be done at the first prenatal visit in partnership with the pregnant woman. Patients who use medications during pregnancy represent a diverse group, and it is important to recognize and differentiate between medications use in the context of medical care, medications misuse, and untreated medications use disorder. Multidisciplinary long-term follow-up should include medical, developmental, and social support. Infants born to women who used medications during pregnancy should be monitored for neonatal abstinence syndrome by a pediatric care provider. Early universal screening, brief intervention (such as engaging a patient in a short conversation, providing feedback and advice), and referral for treatment of pregnant women with medications use and medications use disorder improve maternal and infant outcomes. In general, a coordinated multidisciplinary approach without criminal sanctions has the best chance of helping infants and families.

**KEYWORDS:** Screening- Medications – Pregnant- substance – prenatal.

## INTRODUCTION

Medications use disorder is a pattern of medications use characterized by tolerance, craving, inability to control use, and continued use despite adverse consequences. Medications use disorder is a chronic, treatable disease that can be managed successfully by combining medications with behavioral therapy and recovery support<sup>[5]</sup>, which enables those with medications use disorder to regain control of their health and their lives. Short-term treatment programs aimed at abstinence are associated with high relapse rates<sup>[11]</sup> and generally do not facilitate patients' stable long-term recovery.<sup>[5]</sup>

This underscores the importance of availability and access to ongoing care in medications treatment programs.

A diagnosis is based on specific criteria such as unsuccessful efforts to cut down or control use, as well as use resulting in social problems and a failure to fulfill obligations at work, school, or home.<sup>[12]</sup> The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), replaced the terms medications abuse and medications dependence with the term medications use disorder. The DSM-5 outlines 11 main symptoms of medications use disorder and defines the severity of the disorder based on the number of recurring symptoms experienced within a 12-month period. Severity is classified as mild (two to three symptoms), moderate (four to five symptoms), and severe (six or more symptoms).<sup>[13]</sup> The abuse and dependence terminology do not correlate precisely to the new categories of mild, moderate, and severe medications use disorder. Although this diagnostic terminology has changed, much of the prior research, recommendations, and regulatory requirements in this field rely on the previous terminology, such as abuse and dependence; therefore, those terms are still used when referencing those sources.

Role of the Obstetrician-Gynecologist and Other Obstetric Care Providers Patients who use medications during pregnancy represent a diverse group, and it is important to recognize and differentiate between medications use in the context of medical care (for chronic pain or for addiction), medications misuse, and untreated medications use disorder. To combat the medications epidemic, all health care providers need to take an active role. Appropriate prescribing of medications is vitally important. Before prescribing medications for their patients, obstetrician-gynecologists and other health care providers should do the following.

Ensure that medications are appropriately indicated. For women, including pregnant women, with an medications use disorder, medications agonist pharmacotherapy is the recommended therapy. For chronic pain, practice goals include strategies to avoid or minimize the use of medications for pain management, highlighting alternative pain therapies such as nonpharmacologic (eg, exercise, physical therapy, behavioral approaches) and nonmedications pharmacologic treatments.

Discuss the risks and benefits of medications use and review treatment goals with the patient at the outset. This discussion should include the risk of becoming physiologically dependent on medications and, in the case of pregnant women, the possibility of an infant developing neonatal abstinence syndrome (NAS) (see Neonatal Abstinence Syndrome). However, health care providers should not hesitate to prescribe medications based on a concern for neonatal abstinence syndrome alone.

Take a thorough history of substance use and review the Prescription Drug Monitoring Program, currently operational in 49 states and the District of Columbia. The Prescription Drug Monitoring Program is a valuable resource to determine whether patients have received prior medications prescriptions or other high-risk medications such as benzodiazepines, and should be consulted when patients request medications pain medication or when medications misuse is suspected. This resource (available at [www.pdmpassist.org/content/state-profiles](http://www.pdmpassist.org/content/state-profiles)) can guide safe prescribing and help identify patients who suffer from medications misuse or medications use disorder and who would benefit from treatment. Several states now require that health care providers use Prescription Drug Monitoring Programs before prescribing certain controlled substances.

Before initiating medications therapy for chronic pain for reproductive-aged women, clinicians should discuss family planning and how long-term medications use might affect care during a future pregnancy.

Finally, a cautious approach to prescribing medications should be balanced with the need to address pain in the pregnant woman. Pregnancy should not be a reason to avoid treating acute pain because of concern for medications misuse or NAS.

Obstetric care providers need to be knowledgeable about the medical, social, and legal consequences that can accompany medications use by pregnant women. Pregnancy provides

an important opportunity to identify and treat women with substance use disorders. Identifying patients with substance use disorders using validated screening tools, offering brief interventions (such as engaging a patient in a short conversation, providing feedback and advice), and referring for specialized care, as needed, are essential elements of care<sup>[14]</sup> (Box 1). Additionally, it is important to advocate for this often-marginalized group of patients, particularly in terms of working to improve availability of treatment and to ensure that pregnant women with medications use disorder who seek prenatal care are not criminalized. Finally, obstetric care providers have an ethical responsibility to their pregnant and parenting patients with substance use disorder to discourage the separation of parents from their children solely based on substance use disorder, either suspected or confirmed.<sup>[15]</sup>

In states that mandate reporting, policy makers, legislators, and physicians should work together to retract punitive legislation and identify and implement evidence-based strategies outside the legal system to address the needs of women with addictions.<sup>[16]</sup>

### **Physiology and Pharmacology**

Medications diminish the intensity of pain signals and are generally prescribed for the treatment of pain, although cough and diarrhea are other indications for their use. Medications have the additional effect of causing a sense of euphoria, which can lead to their misuse.<sup>[17]</sup> Medications use disorder may develop with repetitive use of any medications, particularly in individuals with an underlying genetic vulnerability. Heroin is a rapidly acting medications that may be injected, smoked, or nasally inhaled.<sup>[18]</sup> Heroin has a short half-life, and to avoid medications withdrawal symptoms, a physically dependent heroin user will need to take multiple doses daily. Prescribed medications such as codeine, fentanyl, morphine, methadone, oxycodone, meperidine, hydromorphone, hydrocodone, propoxyphene, and buprenorphine all have the potential for misuse. These products may be swallowed, injected, nasally inhaled, smoked, chewed, or used as suppositories.<sup>[19]</sup>

The onset and intensity of effect will vary based on how the drug was taken and the formulation; however, all have the potential for causing respiratory depression, overdose, and death. The risk of respiratory depression, overdose, and death is greater for full medications agonists (such as fentanyl) than for partial agonists (such as buprenorphine). Injection of medications also carries the risk of cellulitis and abscess formation at the injection site, sepsis, endocarditis, osteomyelitis, hepatitis B, hepatitis C, and HIV infection. Sharing of snorting implements also has been identified as a risk factor for hepatitis C and other virus

transmission in a group of pregnant women with hepatitis C.<sup>[20]</sup> Regular, long-term use of any medications leads to predictable physiological dependence, which results in symptoms of withdrawal upon discontinuation of the drug.

Typical symptoms of medications withdrawal include generalized pain, muscle pain, nausea, diarrhea, sweating, rhinorrhea, tearing, dilated pupils, tremor, gooseflesh, restlessness, and anxiety. With short-acting medications, such as heroin, withdrawal symptoms may develop within 4–6 hours of use, peak at 1–3 days, and gradually subside over a period of 5–7 days.

For long-acting medications, such as methadone, withdrawal symptoms usually begin within 24–36 hours of use and may last for several weeks. Unlike alcohol withdrawal, medications withdrawal is rarely associated with severe morbidity and can be readily treated.

### **Effects of Medications Use on Pregnancy and Pregnancy Outcome**

The safety of medications during early pregnancy has been evaluated in a number of observational studies. Earlier reports have not shown an increase in risks of birth defects after prenatal exposure to oxycodone, propoxyphene, or meperidine.<sup>[21,22]</sup> An association between first-trimester use of codeine and congenital abnormalities has been found in some studies<sup>[23–25]</sup> but not in others.<sup>[26,27]</sup>

The authors of one retrospective study observed an increased risk of several birth defects with the use of prescribed medications by women in the month before pregnancy or during the first trimester.<sup>[25]</sup>

Another recent observational study found a possible association between use of medications in the first trimester and neural tube defects, although not with codeine use specifically.<sup>[28]</sup> However, methodological problems with these studies exist, with potential for recall bias and confounding. The observed birth defects remain rare and represent a minute increase in absolute risk.

A recent meta-analysis that compared methadone and buprenorphine found no difference between the groups with respect to congenital malformations. In addition, the incidence of anomalies reported were similar to what would be expected in the general population.<sup>[29]</sup> Overall, concern about a potential small increased risk of birth defects associated with medications agonist pharmacotherapy during pregnancy should be weighed against the clear risks associated with the ongoing misuse of medications by a pregnant woman.

During pregnancy, chronic untreated addiction to heroin is associated with lack of prenatal care, increased risk of fetal growth restriction, abruptio placentae, fetal death, preterm labor, and intrauterine passage of meconium.<sup>[30]</sup>

Additionally, untreated addiction is associated with engagement in high-risk activities, such as prostitution, trading sex for drugs, and criminal activities. Such behaviors expose women to STIs, violence, and legal consequences, including loss of child custody, criminal proceedings, or incarceration.

Pregnant women with medications use disorder often suffer from co-occurring mental health conditions, particularly depression, history of trauma, posttraumatic stress disorder, and anxiety. More than 30% of pregnant women enrolled in a substance use treatment program screened positive for moderate to severe depression, and more than 40% reported symptoms of postpartum depression.<sup>[31]</sup> In addition, they are at increased risk of use of other substances, including tobacco, marijuana, and cocaine.<sup>[32]</sup>

These women also often suffer from poor nutrition, and many have disrupted support systems leading to social service needs. Identifying these problems during pregnancy with referral for specialized multidisciplinary care is important to achieve optimal care for these women.

### **Screening for Medications Use in Pregnancy**

Screening for substance use should be a part of comprehensive obstetric care and should be done at the first prenatal visit in partnership with the pregnant woman. Substance use disorders affect women across all racial and ethnic groups and all socioeconomic groups and affect women in rural, urban, and suburban populations. Screening based only on factors such as poor adherence to prenatal care or prior adverse pregnancy outcome can lead to missed cases and may add to stereotyping and stigma.<sup>[33]</sup>

Therefore, it is essential that screening be universal. Before pregnancy and in early pregnancy, all women should be routinely asked about their use of alcohol and drugs, including prescription medications and other medications used for nonmedical reasons. To begin the conversation, the patient should be informed that these questions are asked of all pregnant women to ensure they receive the care they require. Maintaining a caring and nonjudgmental approach, as well as screening when the patient is alone, are important and will yield the most inclusive disclosure. Obstetric care providers should protect patient

autonomy, confidentiality, and the integrity of the patient-physician relationship to the extent allowable by laws regarding disclosure of substance use disorder (available at [www.guttmacher.org/state-policy/explore/substance-abuse-during-pregnancy](http://www.guttmacher.org/state-policy/explore/substance-abuse-during-pregnancy)).

Physicians should be aware that reporting mandates vary widely and should be familiar with the legal requirements within their state or community.<sup>[15]</sup> Routine screening should rely on validated screening tools, such as questionnaires including 4Ps, NIDA Quick Screen, and CRAFFT (for women 26 years or younger) (Box 2).<sup>[34–36]</sup> These tools have been well studied and demonstrate high sensitivity for detecting substance use and misuse. They can be used in direct interview format by physicians as well as nonphysicians and can be streamlined into clinical practice by using computer-based approaches.<sup>[33]</sup>

Urine drug testing has also been used to detect or confirm suspected substance use but should be performed only with the patient's consent and in compliance with state laws. Pregnant women should be informed of the potential ramifications of a positive test result, including any mandatory reporting requirements.<sup>[15,16]</sup>

Routine urine drug screening is controversial for several reasons. A positive drug test result is not in itself diagnostic of medications use disorder or its severity. Urine drug testing only assesses for current or recent substance use; therefore, a negative test does not rule out sporadic substance use. Also, urine toxicology testing may not detect many substances, including synthetic medications, some benzodiazepines, and designer drugs.

False-positive test results can occur with immune-assay testing and legal consequences can be devastating to the patient and her family. Health care providers should be aware of their laboratory's test characteristics and request that confirmatory testing with mass spectrometry and liquid or gas chromatography be performed as appropriate. Some centers have implemented universal urine toxicology screening for pregnant patients, with one study finding improved rates of detection of maternal substance use compared with standard methods.<sup>[37]</sup>

However, this study did not use validated verbal screening tools in the comparison group, which limits the usefulness of these results. Additional research is needed to better understand the effects of universal urine screening on maternal and neonatal outcomes. For these reasons, validated verbal screening tools such as those discussed previously are the

preferred method for initial screening. History-taking and verbal screening tools provide the opportunity for the prenatal care provider to offer a brief intervention (such as engaging a patient in a short conversation, providing feedback and advice), to educate patients and use principles of motivational interviewing to bring about a desire to change high risk behaviors, when appropriate.<sup>[33]</sup> More severe substance use disorders warrant a referral to specialized treatment.

Obstetric care providers should be knowledgeable about local resources for substance use treatment. Enlisting the help of social service agencies to facilitate patient referral and communicating with substance use treatment health care providers optimize patient care.

## **Treatment**

### **Opioid Agonist Pharmacotherapy**

Since the 1970s, opioid agonist pharmacotherapy (also referred to as medication-assisted treatment), with methadone in combination with counseling and behavioral therapy, has been the standard treatment of heroin addiction during pregnancy.<sup>[30]</sup> In later years, pharmacotherapy with either methadone or buprenorphine has been used for treatment of opioid use disorder<sup>[30,38]</sup> in pregnant women.

The rationale for opioid agonist pharmacotherapy during pregnancy is multifold. Opioid agonist pharmacotherapy prevents opioid withdrawal symptoms and is shown to prevent complications of nonmedical opioid use by reducing relapse risk and its associated consequences. It also improves adherence to prenatal care and addiction treatment programs. Opioid agonist pharmacotherapy in combination with prenatal care has been demonstrated to reduce the risk of obstetric complications.<sup>[30,39]</sup> Neonatal abstinence syndrome is an expected and treatable condition that can follow prenatal exposure to opioid agonists and requires collaboration with the pediatric care team for care of the infant.

Health care providers of addiction treatment should be familiar with the federal regulations regarding Confidentiality of Alcohol and Drug Abuse Patient Records. These regulations require specific elements (42 CFR Part 2) for written consent to disclose patient information.<sup>[40]</sup>

### **Methadone**

Methadone is dispensed on a daily basis by a registered opioid treatment program and should be part of comprehensive treatment, including addiction counseling, family therapy, nutritional education, and other medical and psychosocial services as indicated for pregnant women with opioid use disorder. Maternal methadone dosages are managed by addiction treatment specialists within registered opioid treatment programs, and communication between the obstetric team and the opioid treatment program facilitates good care. The methadone dosage may need to be adjusted throughout the pregnancy to avoid withdrawal symptoms, which include drug cravings, abdominal cramps, nausea, insomnia, irritability, and anxiety. Methadone has significant pharmacokinetic interactions with many other medications, such as antiretroviral agents, and can prolong the QTc interval in a dose-related fashion, which should be considered before new medications are introduced.

If a woman has been treated with a stable methadone dose before pregnancy, pharmacokinetic and physiologic changes that occur during pregnancy may require dose adjustments, especially in the third trimester.<sup>[42]</sup> Because of metabolic changes in pregnancy, a single daily dosage may not control withdrawal symptoms over a 24-hour period. Rapid metabolism often develops during pregnancy, especially in the third trimester and in these cases, split dosages may be optimal.<sup>[43]</sup> Not all women require dose increases during pregnancy, and dosage adjustments should be made on a clinical basis.

If a woman begins treatment with methadone while pregnant, her dosage should be titrated until she is asymptomatic in accordance with safe induction protocols. An inadequate maternal methadone dosage may result in mild to moderate opioid withdrawal signs and symptoms that may cause fetal stress and maternal drug cravings<sup>[43]</sup>, which increase the likelihood of relapse and treatment discontinuation.

Several studies have examined the extent to which the maternal methadone dosage is related to the severity of neonatal abstinence syndrome. A systematic literature review and meta-analysis concluded that the incidence and duration of neonatal abstinence syndrome do not differ based on the maternal dosage of methadone treatment<sup>[44]</sup>; therefore, attempts to minimize the methadone dose are not indicated as low doses are not consistently associated with milder or shorter NAS symptoms. Interestingly, some studies find lower rates of NAS when split dosing regimens of methadone are used.<sup>[43]</sup>

In most situations, pregnant women initiate methadone induction in a licensed outpatient opioid treatment program. Some obstetric services initiate opioid agonist therapy with methadone or buprenorphine in an inpatient setting. Although this may allow closer monitoring of medication response, it is not always necessary or available.

In cases when a pregnant woman initiates methadone treatment as an inpatient, an arrangement should be made before discharge for next-day admission to an opioid treatment program so that there are no missed days. Patients started on buprenorphine as an inpatient may receive a prescription until their appointment with a licensed buprenorphine prescriber. Identification of the ongoing buprenorphine provider and scheduling of an appointment should be done before discharge.

With the exception of buprenorphine, it is currently illegal for a physician to write a prescription for any other opioids, including methadone, for the treatment of opioid use disorder outside of a licensed opioid treatment program (where medications are dispensed).<sup>[45]</sup> Buprenorphine is the only opioid agonist currently approved for the treatment of opioid use disorder by prescription in an office-based setting.<sup>[46]</sup> However, methadone and buprenorphine may be dispensed in a hospital setting by physicians without waivers. Prescribers should be familiar with federal regulations (available at [www.gpo.gov/fdsys/pkg/CFR-2016-title21-vol9/xml/CFR-2016-title21-vol9-sec1306-07.xml](http://www.gpo.gov/fdsys/pkg/CFR-2016-title21-vol9/xml/CFR-2016-title21-vol9-sec1306-07.xml)) and state regulations regarding prescribing of medications for the treatment of opioid use disorder.

### **Buprenorphine**

Recent evidence supports the use of buprenorphine for opioid use disorder treatment during pregnancy. Buprenorphine acts on the same mu-opioid receptors as heroin and morphine<sup>[47]</sup>, but functions as a partial rather than full agonist, making overdose less likely.<sup>[48]</sup> Other advantages of buprenorphine over methadone include fewer drug interactions, the ability to be treated on an outpatient basis without the need for daily visits to an opioid treatment program, and evidence of less need for dosage adjustments throughout pregnancy.

In addition, several trials demonstrate evidence of less-severe neonatal abstinence syndrome.<sup>[49]</sup> The disadvantages, compared with methadone, include rare reports of hepatic dysfunction, the lack of long-term data on infant and child effects, potentially more risks

associated with induction because of the risk of precipitated withdrawal, and an increased risk of diversion (ie, sharing or sale) of prescribed buprenorphine.<sup>[50]</sup>

Buprenorphine is available as a mono-product or in a combined formulation with naloxone, an opioid antagonist, used to reduce diversion because buprenorphine combined with naloxone causes severe withdrawal symptoms when injected. However, naloxone is not orally active, so withdrawal symptoms do not occur when used sublingually as directed.<sup>[47]</sup> The buprenorphine monoprodut has been recommended during pregnancy to avoid any potential prenatal exposure to naloxone, especially if injected.<sup>[50]</sup>

However, recent studies that evaluated the use of the combination product buprenorphine with naloxone found no adverse effects, and outcomes were similar when compared with buprenorphine alone.<sup>[51,52]</sup> The use of the combination product during pregnancy will likely expand as more safety data are accumulated.

### **Postpartum Care**

Breastfeeding is beneficial in women taking methadone or buprenorphine and has been associated with decreased severity of neonatal abstinence syndrome symptoms, less need for pharmacotherapy, and a shorter hospital stay for the infant.<sup>[72]</sup>

In addition, breastfeeding contributes to attachment between a woman and her infant, facilitates skin-to-skin care, and provides immunity to the infant. Breastfeeding should be encouraged in women who are stable on their opioid agonist, who are not using illicit drugs, and who have no other contraindications, such as HIV infection.<sup>[73,74]</sup>

Women should be counseled about the need to suspend breastfeeding in the event of a relapse. The American Academy of Pediatrics recommends breastfeeding for women taking methadone and buprenorphine regardless of maternal dose, as transfer of these medications into breast milk is minimal.<sup>[75]</sup> In nursing women, the ultra-rapid conversion of codeine to morphine can result in high and unsafe levels of morphine in blood and breast milk. The U.S. Food and Drug Administration has strengthened the label warning to state that breastfeeding is not recommended while using medicines containing codeine or tramadol because of the potential for serious adverse effects in the infant due to opioid overdose.<sup>[76]</sup>

However, if a codeine-containing medication is considered the preferred choice, the risk and benefits of this drug and the reasoning behind the FDA warning should be discussed with each family.

Although most pregnant women who take methadone will experience dosage increases during pregnancy, and a need for dosage reduction might be expected postpartum, one study demonstrated little need for immediate postpartum methadone dosage reduction.<sup>[77]</sup>

Significant dose reductions postpartum should not be done routinely but should be titrated to signs and symptoms of sedation, particularly at the peak of the dose (2–6 hours). Most women taking buprenorphine will not experience large dosage adjustments during their pregnancies and most may continue the same dosages after delivery.<sup>[77]</sup> Other medications that can produce sedation (eg, benzodiazepines, zolpidem, antihistamines) should be used with caution, as they may add to the risk of maternal respiratory depression.<sup>[78]</sup>

## CONCLUSION

Early universal screening, brief intervention (such as engaging a patient in a short conversation, providing feedback and advice), and referral for treatment of pregnant women with opioid use and opioid use disorder improve maternal and infant outcomes. Contraceptive counseling and access to contraceptive services should be a routine part of substance use disorder treatment among women of reproductive age to minimize the risk of unplanned pregnancy. Pregnancy in women with opioid use disorder should be co-managed by the obstetric care provider and a health care provider with addiction medicine expertise, and appropriate 42 CFR Part 2-compliant consent for release of information should be obtained from the patient to allow exchange of information between the health care providers. Given the unique needs of pregnant women with an opioid use disorder, health care providers will need to consider modifying some elements of prenatal care (such as expanded STI testing, additional ultrasound examinations to assess fetal weight if there is concern for fetal growth abnormalities, and consultations with various types of health care providers) in order to meet the clinical needs of the patient's particular situation. Continuity of care, including ensuring consistent daily dosing of buprenorphine or methadone, is critical to success. For women, including pregnant women, with an opioid use disorder, opioid agonist pharmacotherapy is the recommended therapy and is preferable to medically supervised withdrawal because withdrawal is associated with higher relapse rates, which lead to worse outcomes.

More research is needed to assess the safety (particularly regarding maternal relapse), efficacy, and long-term outcomes of medically supervised withdrawal. Infants born to women who used opioids during pregnancy should be monitored by a pediatric care provider for neonatal abstinence syndrome. Multidisciplinary long-term follow-up should include medical, developmental, and social support. In general, a coordinated multidisciplinary approach without criminal sanctions has the best chance of helping infants and families. Obstetric care providers have an ethical responsibility to their pregnant and parenting patients with substance use disorder to discourage the separation of parents from their children solely based on substance use disorder, either suspected or confirmed.

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