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Chronic opioid use and pregnancy: A critical review of the literature

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REVIEW

Abstract

The present review examines the issue of chronic opioid use during pregnancy based on recently published articles on the topic. Opioids are a group of endogenous and exogenous substances, prototypical analgesic, antitussive and antidiarrheal drugs indicated for pain management by inhibiting pain-related stimuli at opioid receptors in the nervous system. In pregnancy, on the other hand, each stage must ensure that women and their babies reach their full potential for health and well-being despite any difficulties such as prevailing manifestations of negative psychological symptomatology, especially anxiety, stress and depression. The focus of this review is to examine pain management in pregnancy, by assessing and emphasizing the importance of balancing the risks of complications for pregnant women and the fetus, through screening for substance use during pregnancy, access in drug and psychiatric treatment during pregnancy and postpartum, prevention and management of withdrawal syndrome for infants prenatally exposed to substances, and multidisciplinary, long-term follow-up care for mothers and infants. The incidence of prescription of opioids in pregnancy in different countries is reported, as are the physical and psychological risks to mothers and babies of untreated opioid use disorder in pregnancy. Attention is also given to whether the management of the complications of opioid use disorder in pregnant women is not always directly undertaken by specialists, mainly due to their severity. Prevailing treatment options for the specific disorder in pregnant women are analyzed therapeutically, such as the preference for maintenance treatment with long-acting opioids (e.g., methadone or buprenorphine), and the avoidance of detoxification due to the possibility of miscarriage or premature birth. More specifically, a discussion is made on whether methadone, buprenorphine, and more recently recommended buprenorphine in combination with naloxone should be the main options for the treatment of opioid use disorder during pregnancy, while a discussion is made on methadone or buprenorphine maintenance treatment in combination with breastfeeding which is recommended mostly also after the end of pregnancy. At the same time, the possibility of questioning the criteria for separating pregnant women who use opioids from typical pregnant women and factors contributing to the inclusion of these women in therapies, such as consolidating effective strategies for the primary prevention of opioid use and its complications, optimizing care coordination among services and creating a safe environment where women's own experiences will be acknowledged are additional topics that will be reviewed through a critical lens.

Key – words: pregnancy, opioid use disorder, methadone – buprenorphine, psychopharmacology.

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Introduction

Although people used psychoactive substances long before the advent of psychiatry, the past 50 years could arguably be characterized as the era of psychopharmacology[1]. From the prehistory of modern psychopharmacology and its golden age with the discovery of the modern classes of psychotropic drugs to its influence on the way illness and its treatment are treated today, the heyday of mainstream antidepressants and antipsychotics has changed the data of mental illness[2]. Of course, as these data change, so do the overall benefits of psychotropic drugs[1], especially when associated with unmet mental health needs and psychological pain[3].

Of course, opioid use disorders in pregnant women rarely constitute medical emergencies, but rather provide opportunities for life-changing interventions[4].

Opioids are the prototypical analgesic, antitussive, and antidiarrheal drugs primarily indicated for pain management (e.g., hyperalgesia and analgesia)[5]. It is a group of endogenous and exogenous substances that provide analgesia, through the inhibition of pain-related stimuli at the opioid receptors in the nervous system[6]. Some of these are naturally occurring opium alkaloids (e.g., codeine and morphine), while others are semi-synthetic forms of natural opioids (e.g., heroin and oxycodone) or fully synthetic (e.g., methadone and fentanyl). Furthermore, they are separated based on their mu opioid receptor (MOR) activity as pure agonists or partial agonists. Most opioids used for analgesia are full agonists, while some agonists, such as buprenorphine, have lower endogenous activity at these receptors. Opioids can be administered orally, intranasally, intravenously, transdermally[7], by inhalation, sublingually, subcutaneously, and rectally[6].

In practice, they activate the central and peripheral opioid receptors mu (MOR), kappa (KOR), and delta (DOR), which have a common analgesic effect, but unique effects on the brain circuits. MOR receptors bind endorphins and trigger euphoria, physical dependence, respiratory depression, and the impulsive properties of reward stimuli (goal-directed behavior)[8]. KOR receptors bind to dynorphins and produce discomfort and sedation9, while DOR receptors bind to enkephalins and cause anxiolytic effects8. The psychoactive properties of opioids at these receptors, mainly euphoria and sedation, often provide the basis for non – medical use[10]. Due to their increased potential for abuse, these drugs are often used in such a way that a large number of patients develop dependence, which forces them to continue using them in order to recreate the pleasure of the first time[11].

Pregnancy, for its part, is unique and each stage (should) be a positive experience, ensuring that women and their babies reach their full potential for health and well-being despite any difficulties[12]. Of course, it can be a period of prenatal psychological distress, with manifestations of negative psychological characteristics, especially anxiety, stress and depression predominating[13]. The convergence of these three relatively distinct psychological dimensions[13], may precipitate psychiatric symptoms, especially if the person is vulnerable to their mental health, as happens during pregnancy[14]. In fact, if a mental illness, such as depression[15], is not treated because the woman decides to discontinue psychotropic treatment before or immediately after conception, there may be an increased risk of relapse[16]. At the same time, women may experience pain from normal changes of pregnancy (e.g., round ligament pain), recurrence of chronic conditions (e.g., back pain), or pathological pain associated with new conditions (e.g., appendicitis)[17].

However, these arise more in cultures where the fear of responsibility for the undesirable outcome of childbirth overestimates this risk and promotes the excessive use of technological innovations for treatment, even when they are not confirmed by research[18]. Opioid use during pregnancy is associated with adverse birth outcomes, likely resulting from the complications of unfortunate life circumstances[19] and the presence of comorbid medical and psychiatric conditions such as alcohol use[20], smoking, depression, stress, anxiety, and multiple substance use[15]. Pain management in pregnancy must therefore balance the risks of complications for the pregnant woman as well as for the fetus17, through screening for substance use during pregnancy, access to pharmaceutical and psychiatric treatment during pregnancy and postpartum, prediction and management of deprivation syndrome for infants prenatally exposed to substances, and multidisciplinary, long-term follow-up care for mothers and infants[21-22].

Theoretical background

Historically, Europe has led the world in consumption of brand-name drugs. According to the European Monitoring Center for Drugs and Drug Addiction, 73 still unknown psychoactive substances were released on the European markets in 2012 alone[23]. This data is constantly changing, with the number of new brand-name drugs appearing first in the United States dominating the last few years. In 2015, 240 million opioid prescriptions were filled, nearly one for every adult in the general population, in the United States alone[24], while in 2017, nearly 60 opioids were prescribed for every 100 people in the United States[6]. Most such prescriptions are indicated for the treatment of severe acute, cancer, and postoperative pain[25], but also for end-of-life care[26]. However, there has also been a significant increase in opioid prescriptions in patients with chronic non-cancer pain[6], even though their role in the treatment of chronic, non-malignant pain is less clear[27-28]. In these patients, opioids are often prescribed in larger amounts and for longer durations compared to initial assessment, resulting in harm[29].

In addition, individuals who abuse opioids are distinguished as those who receive prescription opioids for the treatment of inadequately treated chronic pain (interruption, reduction, or continuation)[26], or are exposed to opioids during an acute pain episode, although they are prone to abuse opioids, or use opioids for recreational use and relief of psychological and / or emotional stress without medical supervision[30]. Thus, along with the use of prescription opioids in recent years, the abuse of prescription opioids and heroin has increased, demonstrating that people who abuse prescription drugs may turn to illicit heroin use. In fact, the average number of opioid-related deaths has increased by more than 20% from 2011 – 2016, with the increase being most pronounced in the United States, Canada, Sweden, Norway, Ireland, England and Wales[24], and population groups, such as pregnant women, facing equally problematic opioid use that potentially leads to maternal or fetal death[31].

Opioid use in pregnancy, in particular, has increased in parallel with the increase in opioid use seen in the general population[6], as recorded opioid use disorder in hospital delivery, for example, in the US has overall quadrupled between 1999 and 2014[32]. Prescription opioid use is common during pregnancy[33], with women receiving opioids either for the diagnosis of acute or chronic pain or as substitution therapy for opioid use disorder[34]. In 2014, 14.4% of pregnant women in the US were exposed to prescription opioids at some point during pregnancy, with approximately 6% of women exposed during each trimester[35]. Accurate data on the prevalence of illicit drug use among pregnant women are not available for most European countries, but mostly show similar patterns to those in the United States[36]. This fact poses a significant public health concern for both mothers and their children, since it increases the risk of adverse birth outcomes and related complications[37].

Opioid use disorder

Opioid use disorder, as a global phenomenon that also affects women of reproductive age[38], is defined, in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM)[39], as a problematic pattern of opioid use that leads to clinically significant harm or distress, as manifested by at least two of a range of diagnostic criteria, occurring within a 12-month period. Chief among these are those characterized by a pattern of strong desire or urge to use opioids, tolerance, withdrawal, and inability to control use despite adverse consequences. Tolerance, which corresponds to the significantly increasing amounts of opioids to achieve intoxication or the same desired effect[39], is achieved within days and the withdrawal syndrome is severe40. In withdrawal, opioids (or a closely related substance) are taken to alleviate or avoid withdrawal symptoms[41].

Of course, the diagnosis must take into account whether the person is in early remission, e.g., with 3 months, or in prolonged remission, with 12 months or more without meeting criteria (except for desire), or in maintenance therapy, or in controlled environment (where access to opioids is limited)[39]. In other words, opioids prescribed for mild to moderate acute pain are taken indefinitely, with no intention to reduce or stop use[40]. Of course, due to their pharmacological effects, opioids are highly addictive[42]. Chronic opioid use results in alterations in receptor sensitivity, leading to drug tolerance and withdrawal[43]. Pain perception becomes disproportionate to the stimulus (hyperalgesia) in those who use or abuse opioids long term. It is worth noting that in 2017, opioid overdose was declared an emergency in the United States[40], with 6.5% of pregnant women reporting illicit use of prescription opioids or heroin in the past year[44]. Approximately 1 in 5 women from 46 US states and Washington, D.C., received prescription opioids during pregnancy, a rate that increased from 18.5% in 2000 to 22.8% in 2007[34].

Physical symptoms during pregnancy

Specifically, individuals with opioid use disorder tend to develop regular patterns of compulsive use of opioid substances that are used for an illegitimate medical purpose or, if there is a medical condition that requires opioid treatment, in doses greater than the amount required for that condition, to a degree where daily activities are designed around the acquisition and administration of opioids[39]. The process of obtaining opioids is facilitated in the illegal market, but they can also be obtained from doctors by falsifying or exaggerating general medical issues or by simultaneously obtaining prescriptions from several doctors[45]. Most people with opioid use disorder have significant levels of tolerance and will experience withdrawal if opioids are abruptly discontinued[46]. They often develop conditioned responses to drug – related stimuli (e.g., a desire to see any substance resembling heroin powder), a phenomenon that occurs with most drugs that cause intense psychological changes. Such responses likely contribute to relapse, are difficult to eradicate, and typically persist long after detoxification is complete[47].

Similarly, untreated opioid use disorder during pregnancy poses significant risks to both mothers and babies: among others, acute maternal withdrawal results in elevated catecholamines, uterine contractions[32], and decreased placental blood flow and oxygen delivery to the infant[48-50]. Fluctuating opioid levels may expose the fetus to repeated episodes of intrauterine deprivation, causing hyperkinetic activity, increased oxygen consumption, and increased norepinephrine levels in the amniotic fluid, a combination that can lead to preterm labor, fetal hypoxia (insufficient oxygen reaching the tissues) or fetal death[32]. Although opioid exposure may adversely affect children's general cognitive functioning, psychomotor and social – emotional behavior, and language, various psychosocial stressors, such as poverty or compromised parenting, are better known to contribute to adverse neurodevelopmental outcomes[51].

Additionally, low birth weight may be observed in infants of mothers with opioid use disorder, but is usually not significant and generally not associated with serious consequences[39]. At the same time, pregnant women who inject drugs are at increased risk of overdose, which is perhaps the most important morbidity associated with opioid use disorder in pregnancy[52]. A typical example of this is when a pregnant woman tries to abstain from use during pregnancy for the benefit of the baby, and immediately after giving birth, uses illegal drugs in the same doses tolerated before the period of abstinence, so she unwittingly overdoses[51].

Psychological symptoms during pregnancy

Pregnant women with opioid use disorder are a subset of women with addiction with unique characteristics and needs, as most face adverse life circumstances, are affected by past and present trauma[53], and have high rates of comorbidity with often more than one mental health disorder[54]. The phenomenon in which multiple symptoms manifest in such a way as to indicate the presence of multiple psychiatric conditions is far from rare[19]. Among the most frequently considered psychiatric disorders in opioid-dependent pregnant women are Major Depressive Disorder, Generalized Anxiety Disorder, Post – Traumatic Stress Disorder (PTSD)[54-55], Dysthymia, Panic Disorder, Hypomania, Agoraphobia, and to a lesser extent Obsessive-Compulsive Disorder[19].

Mental health disorders, including depression and anxiety, appear elevated among hospitalized pregnant women with comorbid cannabis and opioid use disorder56, while depression, PTSD, and tobacco dependence or harmful use predominate in adolescent pregnant women[57]. The association between substance use and mental health issues in obstetric populations is significant[58] and evidenced by the reporting of psychiatric symptoms during treatment (e.g., mood, anxiety, suicidal ideation)[59].

Recommended treatments

Managing the complications of opioid use disorder in a pregnant woman can be daunting for any clinician[49], mainly because they are increased for both mothers and fetuses[16]. There are many times when doctors outside of obstetrics and gynecology are reluctant to provide optimal care to pregnant women with any possible medical complications[60-61]. Therefore, policies that pregnant women with substance use disorders perceive as threatening discourage them from seeking comprehensive medical evaluation, care, and treatment during their pregnancy[22].

Treatment during pregnancy

Opioid treatment during pregnancy has been associated with atypical fetal growth and birth defects, stillbirth, preterm birth, and neonatal opioid withdrawal syndrome[62]. Another finding particularly associated with fetal death, delayed maturation of placental villi, has been observed in placentas exposed to opioid maintenance therapy[32]. However, detoxification during pregnancy is a complicated procedure that is not recommended in several cases63 due to the possibility of miscarriage or premature birth[64]. Therefore, women who enter pregnancy using regular opioids for pain management or for opioid maintenance therapy are maintained on a long-acting opioid (e.g., methadone or buprenorphine)[32].

The preference for treatment with methadone and buprenorphine contributes to the prevention of withdrawal symptoms, stability in everyday life[65], and the management of illegal opioid use in pregnant women66. Moreover, the present treatment has been found to minimize risks[67-68], and improve maternal and fetal outcomes compared to complications seen in untreated opioid abuse[69]. Furthermore, the risks to the mother and fetus from failed detoxification and from relapse to illicit drug use are greater than the corresponding risks from opioid maintenance treatment such as methadone or buprenorphine, which appears to increase the chances of positive pregnancy outcome[70-71]. Pain management during labor should be discussed with the woman and the obstetric team. Besides, methadone is associated with improved prenatal care, reduced maternal morbidity, and improved neonatal outcome. In contrast, buprenorphine has been associated with approximately half the risk of preterm birth, higher birth weight[72], greater head circumference, and fewer neurobehavioral problems in infants, compared with methadone[73].

A prerequisite for effective methadone or buprenorphine treatment is the establishment of a comprehensive treatment program, with a coordinated team of clinicians, including addiction and behavioral health specialists, obstetricians and gynecologists, and social service providers[74], ideally in conjunction with counseling or behavioral psychotherapy[75]. The choice of methadone or buprenorphine should unquestionably also be based on the individual needs and preferences of the woman with informed consent after a thorough evaluation[20]. The goal of treatment should be to eliminate illicit drug use as early as possible in pregnancy (e.g., first trimester) for those initiating treatment before conception[70], or to prevent relapse to illicit drug use for those already in substitution therapy[16]. Pregnant women already receiving methadone substitution therapy should probably be advised not to switch to buprenorphine because of the risk of withdrawal, particularly to the fetus64, and vice versa[76].

On the contrary, precisely because of this complexity of opioid treatment[77], there are not a few cases where in pregnant women receiving daily opioid treatment, the latter become unnecessary and should be gradually reduced or discontinued[62], if the risk of relapse is low[14]. Methadone can be used in opioid-dependent pregnant women[62], as can monotherapy with buprenorphine, to avoid fetal exposure to naloxone[78]. Clearly, the dose of methadone to be used in pregnancy is a matter of debate: ideally, it would be sufficient to reduce illicit drug use or use the lowest dose to avoid fetal opioid withdrawal syndrome[16]. Similarly, women already taking naltrexone are advised to continue during pregnancy, as the risk of relapse and possible overdose after stopping treatment is greater than the risk of naltrexone exposure to the newborn[79], although they could discontinue it if permitted[80]. The preferred opioid for nursing mothers is morphine, as it secretes the least amount into breast milk compared to other opioids[62].

Establishing treatment programs for pregnant women with opioid use disorder and comorbid psychiatric disorders requires further research, as understanding of the

prevalence and extent of comorbidity and the impact of dual diagnosis on disease severity and treatment outcomes is lacking[54]. During methadone maintenance treatment in pregnant women with comorbid anxiety disorders, mood disorders, and opioid use disorder, women with anxiety disorders were more likely to adhere to follow – up treatment than women with mood disorders, so treatment was not maintained, while higher incidence of suicidal ideation was reported[81]. In another clinical trial with methadone and buprenorphine in pregnant opioid – dependent women, anxiety symptoms were positively associated with antepartum treatment discontinuation, whereas depressive symptoms did not show such evidence[82].

When a probable diagnosis of major depressive disorder is made, at least one type of medication is prescribed. The most common drug class is anxiolytics, followed by selective serotonin reuptake inhibitors (SSRIs), although mixed neurotransmitter reuptake inhibitors, tricyclics, antipsychotics, and mood stabilizers may also be used[19]. Data on the association of SSRIs with significant neonatal malformations are limited[83], but infants exposed to them prenatally may have an increased likelihood of needing pharmacological treatment of neonatal opioid withdrawal syndrome[84] and experience long – term effects on their motor control[85]. Therefore, a comprehensive discussion of the maternal and neonatal risks and benefits of using psychiatric pharmacotherapy in pregnancy should take place before initiation[86].

Overall, methadone, buprenorphine and more recently recommended buprenorphine in combination with naloxone are now the main options for the treatment of opioid use disorder during pregnancy[87]. Buprenorphine in combination with the opioid antagonist naloxone acts advantageously to reduce misuse and diversion in pregnant women and has a lower severity of opioid withdrawal syndrome in neonates. It is also worth noting that naloxone prescription programs are often an integral part of overdose prevention care for pregnant women who inject drugs[52]. Highlights of such programs include airway maintenance, use of fixed – dose naloxone when the respiratory rate is 12 or less, and transfer to a maternity unit for ongoing monitoring. The reason such programs are organized in this way is primarily to allow monitoring of maternal and fetal status, as well as to provide patients with the opportunity to participate in opioid use disorder treatment if they so desire[68].

Treatment after pregnancy

Women with an opioid use disorder may require larger amounts of pain medication postpartum compared to women without such experience with opioids[88-89]. Especially in the cases of women who do not use other substances and are maintained on methadone or buprenorphine treatment, breastfeeding can encourage and promote the mother – infant bond and probably have mitigating effects on the severity of the neonatal withdrawal syndrome[80]. The severity of the latter may be less with buprenorphine than with methadone[90]. However, other factors such as maternal use of tobacco or benzodiazepines, treatment regimens, and hospital protocols that determine where infants reside (e.g., neonatal intensive care unit) may alter this relationship88. Breastfeeding, however, should be avoided in pregnant women who actively use heroin and other illicit drugs[91], as it can cause tremors, restlessness, vomiting, respiratory depression, lethargy, and underfeeding in infants[89].

Along with methadone or buprenorphine maintenance therapy, additional doses of short – acting oral or intravenous opioids may be necessary for women after cesarean section, while oral and injectable nonsteroidal anti-inflammatory agents are often sufficient after vaginal delivery[89]. In fact, women treated with buprenorphine show increased pain but no increase in opioid use after vaginal delivery, but an increase in pain and opioid use after caesarean section[92]. Methadone-maintained women have similar analgesic needs and response during both of these deliveries, but require more opioids after caesarean section[93]. Thus, there is a need to establish changes in the dosage of agonist drugs also in the postpartum period, although the response of pregnant women to switching from buprenorphine to methadone appears variable[94], given that their life circumstances may also be variable[95].

Discussion – Future suggestions

Looking at the above, one could first point out how meeting 11 criteria for DSM – 5 Opioid Use Disorder reduces people to “addicts”. It therefore produces a stigmatizing identity, a type of person – the addict – defined in terms of pathological desires[96]. Individuals who receive treatments based on their eligibility criteria in DSM – 5 are defined as having severe opioid use disorder, a label that itself is stigmatizing. An inevitable result of this is that programs using DSM – 5 for eligibility criteria treat participants as individuals with disorders rather than as individuals with everyday experiences and practices far beyond the boundaries of the specific criteria[97]. After all, a person diagnosed with a disorder is potentially considered to be in a condition, so it becomes more difficult to reverse it, especially when it comes to a pregnant woman whose suitability as a mother and caregiver may be questioned if she has such a diagnosis[98].

At the same time, it cannot be overlooked that some of the DSM-5 criteria for opioid use disorder are closely related to socio – structural issues, such as participation in illegal activities to secure monetary remuneration, unstable housing or the lack of it, clashes with police officers and imprisonment[97]. Pregnant women are at high risk for sexual violence, homelessness, prostitution and incarceration, and many of them are not in a safe drug – free living environment for themselves or their children[89]. The concern here is the confounding of drug effects with the political, socio – structural and cultural factors that lead to drug – related harm. The stigmatization of an often lifelong

exposure to gendered / racial / structural violence is again addressed as the focus shifts away from these factors, but also from the wider policies that favor drug use and thus addiction in a particular era[99]. Thus, drug use is isolated, rather than recognizing how it is connected to other issues, such as stigma, institutional neglect, criminalization, marginalization, poverty, violence, isolation, and separation from the newborn[100], which are not referenced in DSM – 5[97].

Furthermore, the role of differences, for example between US states, in clinical and surveillance definitions for coding and functioning, screening and treatment efforts specific to pregnant women[101], and existing policies, including criminal penalties for substance use during pregnancy[60] or the risk of loss of parental rights[102] is important. Equally important is the possible use of non-opioid substances (barbiturates or benzodiazepines), which may contribute to opioid withdrawal syndrome in fetuses, as well as the 1.4% of pregnant women reporting opioid abuse in the month before delivery (heroin use or abuse of prescription painkillers), in contrast to only 0.8% of recorded maternal opioid-related diagnoses during labor in the study by Hirai, Ko, Owens, Stocks, and Patrick[103]. In general, well – controlled studies, e.g., randomized clinical trials, are absent from the literature, which should be extended beyond the triage between methadone or buprenorphine for the treatment of pregnant women with opioid use disorder[104].

Therefore, given the ongoing epidemic of illicit drug overdose death in the United States, Canada, and other countries and the criticality for immediate action, challenging the DSM – 5 criteria for opioid use disorder, drug prohibition, and of contractual cases for people who make use of them, is valued as an imperative[97]. The associated medical complications of opioid use disorder in pregnancy are serious, but many options exist for the primary prevention of complications, morbidity, and mortality[52]. Thus, future research is needed to clarify the safety of alternative opioids, to define prescribing guidelines at the time of delivery, but also throughout pregnancy[17] and to educate and inform specialists, providers and the general population[105].

Ultimately, until the establishment of effective strategies for the primary prevention of opioid use and its complications, it must be ensured that clinicians take advantage of every opportunity to prevent morbidity in pregnant women and fetuses[52], and that medication, possibly in combination with psychiatric treatment and care coordination services[106] to ensure a safe and supportive living environment during the initial antenatal care visit and afterwards[89]. It is about the effort to include the voices of women themselves, as they are primarily responsible for their experiences and their management[60].

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