REVIEW ARTICLE

Substance use disorder in pregnancy: A review

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ABSTRACT

Substance use during pregnancy presents substantial challenges to both maternal and fetal health. In recent years, nearly 1 in 3 pregnancies in North America were impacted by substance use, regardless of level or type of substance involved. From 2017 to 2019, nearly 20% of all maternal deaths in Ontario and British Columbia were related to drug overdose. Opioids, alcohol, and stimulants are among the most misused substances. Managing substance use disorders in pregnancy requires a comprehensive understanding of pregnancy physiology, pharmacology of the substance involved, its effects on maternal and fetal health, as well as post-partum care considerations. In this article, we provide an evidence-based review of opioid, alcohol, and stimulant use disorders in pregnancy, examining risks, maternal and fetal implications and management strategies. We recognize that nicotine, tobacco, and marijuana use also pose significant risks in pregnancy, however they are beyond the scope of this review.

KEYWORDS: substance use; pregnancy; alcohol; addiction; perinatal; obstetrical; stimulants; opioids

RÉSUMÉ

L'utilisation de substances psychoactives pendant la grossesse pose des problèmes importants pour la santé de la mère et du fœtus. Ces dernières années, près d'une grossesse nord-américaine sur trois était touchée par l'utilisation de substances psychoactives, quel que soit la quantité ou le type utilisé. De 2017 à 2019, près de 20 % de tous les décès de mères en Ontario et en Colombie-Britannique étaient attribuables à des surdoses. Les opioïdes, l'alcool et les stimulants font partie des substances dont on abuse le plus. Pour prendre en charge des troubles liés à une substance pendant la grossesse, il faut posséder une profonde compréhension de la physiologie de la grossesse, de la pharmacologie de la substance en cause, de ses effets sur la santé de la mère et du fœtus et des questions relatives aux soins postnatals. Le présent article contient une analyse fondée sur des données probantes des troubles liés à l'utilisation d'opioïdes, d'alcool et de stimulants pendant la grossesse et propose un examen des risques, des conséquences pour la mère et le fœtus et des stratégies de prise en charge. La consommation de nicotine, de tabac et de marijuana constitue également un risque marqué pendant la grossesse, mais elle dépasse la portée de la présente analyse.

MOTS-CLÉS : utilisation de substances psychoactives; grossesse; alcool; dépendance; périnatal; obstétrical; stimulants; opioïdes

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KEY POINTS

- Managing substance use disorders in pregnancy requires a comprehensive, multidisciplinary approach.
- While buprenorphine/naloxone combination therapy is favoured because of its safety profile, methadone is used for individuals with high opioid tolerance or severe opioid use disorder.
- Naltrexone monotherapy is considered safe during pregnancy but rarely used as it requires a 7-day abstinence period, which can precipitate withdrawal.
- Slow-release oral morphine is comparable to methadone for risk of neonatal withdrawal, and use is typically reserved to adjunctive therapy with methadone.
- Treatment of low-level alcohol use during pregnancy is predominantly non-pharmacological.
- Contingency management, cognitive behavioural t and the Matrix Model are evidence-based modalities for treating stimulant use disorder during pregnancy.
- Mirtazapine is the safest pharmacologic option for treating stimulant use disorder in pregnancy.

INTRODUCTION

Substance use during pregnancy presents substantial challenges to both maternal and fetal health. In recent years, nearly 1 in 3 pregnancies in North America were impacted by substance use, regardless of level or type of substance involved.[1] From 2017 to 2019, nearly 20% of all maternal deaths in Ontario and British Columbia were related to drug overdose.[2] Opioids, alcohol, and stimulants are among the most misused substances.[1,3] Managing substance use disorders in pregnancy requires a comprehensive understanding of pregnancy physiology, pharmacology of the substance involved, and the effects of the substance involved on maternal and fetal health, as well as post-partum care considerations. In this article we provide an evidence-based review of opioid, alcohol, and stimulant use disorders in pregnancy, examining risks, maternal and fetal implications, and management strategies. We recognize that nicotine, tobacco, and marijuana use also pose significant risks in pregnancy; however, they are beyond the scope of this review. We have provided key resources for further information in Table 1.

OPIOID USE DISORDER

Incidence and maternal-fetal outcomes

The incidence of opioid use disorder (OUD) during pregnancy in Canada has significantly increased in recent years, with current estimates suggesting that 1–2 out of every 100 pregnancies are affected. Prescription opioids (such as oxycodone and hydromorphone) were primarily responsible for opioid overdoses until approximately 2010, after which time restrictions on prescription opioids led to a rise in heroin-related overdose deaths. In 2013 fentanyl analogues rose in prominence and are currently the major driver of overdose-related deaths in North America.[4,5] Pregnancy-related physiologic changes alter the pharmacodynamics of opioids, making withdrawal more common and increasing the risk of overdose-related deaths.[6] These changes include increased circulating blood volume and glomerular filtration rate, reduced plasma protein concentrations, and altered hepatic metabolism.[7] Opioid use during pregnancy is linked to a range of adverse outcomes, including an increased risk of minor congenital malformations,[8] intrauterine growth restriction (IUGR), preterm labour,[9] placental insufficiency, and higher rates of neonatal intensive care unit (NICU) admissions (typically driven by neonatal opioid withdrawal syndrome [NOWS], a known complication of in-utero opioid exposure[9]). Maternal side effects include sedation, dizziness, nausea, vomiting, severe constipation, physical dependence, and respiratory depression. Furthermore, opioid use can exacerbate pre-existing maternal conditions such as chronic respiratory and cardiovascular diseases.[10] NOWS can affect 30%–85% of neonates born to individuals who used opioids during pregnancy.[11] Clinical manifestations of NOWS include irritability, hyperreflexia, seizures, vomiting, diarrhea, poor feeding, and autonomic symptoms, such as excessive sweating, sneezing, and hyperthermia.[6]

Management

Health care providers are cautioned against tapering or de-escalating opioids in pregnant individuals with OUD without transitioning to a long-term maintenance treatment plan.[12] In the non-pregnant population, opioid tapering and de-escalation are linked to higher risks of relapse, transmission of HIV, hepatitis, C and overdose-related deaths.[13] In pregnant individuals, this approach has been associated with significant maternal and fetal distress, including fetal hypoxia, preterm labour, and even fetal mortality.[14,15] Table 1 offers an overview of available national tertiary care centres specializing in OUD in pregnancy.

Non-pharmacologic management

Providers should adopt care models that address the specific motivators and barriers faced by pregnant in-

Table 1. National tertiary-care centres specializing in perinatal addictions and additional key resources

National centres for perinatal addictions		
City	**Centre**	**URL**
Vancouver, British Columbia	Sheway Pregnancy Outreach Program (Vancouver Coastal Health)	https://www.vch.ca/en/service/sheway-pregnancy-outreach-program
Calgary, Alberta	East Calgary Health Centre	https://www.albertahealthservices.ca/findhealth/facility.aspx?id=1036102
Saskatoon, Saskatchewan	PORT·- Prenatal Outreach Resource Team	https://sanctumcaregroup.com/port/
Toronto, Ontario	My Baby and Me Program (Saint Michael's Hospital)	https://unityhealth.to/clinics-services/my-baby-and-me-perinatal-addictions-clinic/
Toronto, Ontario	SUPport - Substance use during pregnancy clinic (Mount Sinai Hospital)	https://www.sinaihealth.ca/areas-of-care/wih/pregnancy-birth-and-newborn-care/substance-use-during-pregnancy-support-clinic
Toronto, Ontario	T-CUP - Toronto Centre for Substance Use in Pregnancy (Saint Joseph's Hospital)	https://www.torontocentralhealthline.ca/displayservice.aspx?id=191638
Kingston, Ontario	Dr. Adam Newman (Queen's University)	https://familymedicine.queensu.ca/patient-care/kingston-fm-ob-call-group
Hamilton, Ontario	PROSPR/IPROSPR (McMaster University)	https://mch.mcmaster.ca/services/prospr/
Montreal Quebec	Programme Rond Point (University of Montreal)	https://pediatriesociale-cs.org/cpsc-centre-sud/nos-services/programme-rond-point/
Halifax, Novia Scotia	Dr. Victoria Allen (Dalhousie University)	https://medicine.dal.ca/departments/department-sites/obstetrics/divisions/maternal-fetal.html
Additional resources		
Resource	**Source**	**URL**
T-ACE	Screening tool for AUD in pregnancy	https://projectteachny.org/app/uploads/2022/07/T-ACE_alcohol_screen.pdf
AUDIT-C	Screening tool for AUD in pregnancy	https://www.hepatitis.va.gov/alcohol/treatment/audit-c.asp
Tobacco and Nicotine Cessation During Pregnancy	ACOG 2023	https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/05/tobacco-and-nicotine-cessation-during-pregnancy
Marijuana Use During Pregnancy and Lactation	ACOG 2021	https://www.acog.org/clinical/clinical-guidance/committeeopinion/articles/2017/10/marijuana-use-during-pregnancy-and-lactation

AUD = Alcohol use disorder; T-ACE = Tolerance, Annoyance, Cut Down, Eye Opener; AUDIT-C = Alcohol Use Disorders Identification Test; ACOG = American College of Obstetricians and Gynecologists

dividuals with OUD.[6] These models are crucial for establishing long-term, therapeutic relationships between patients and healthcare teams. They emphasize delivering care in a non-judgmental, patient-centred, and flexible manner. The foundation of these models is harm reduction, with a focus on trauma-informed and culturally sensitive care.[16] Effective implementation of these models requires a multidisciplinary approach, drawing on the expertise of obstetrical care providers, addiction specialists and a range of allied healthcare professionals, including nursing staff, social workers, nutritionists and occupational therapists.[17,18]

Available literature regarding non-pharmacologic interventions for the treatment of OUD in pregnancy focuses on contingency

management and motivational interviewing.[19] Contingency management uses a predetermined schedule of incentives—vouchers, gift cards, or prizes—that increase in value as participants achieve sustained periods of abstinence, as confirmed by urine drug screening.[20] Motivational interviewing refers to a counselling methodology that aims to strengthen motivation and commitment to reducing or stopping substance use, in an atmosphere of acceptance and compassion.[21] A 2015 Cochrane review assessing the effectiveness of various psychosocial interventions in pregnant individuals enrolled in illicit drug treatment programs found shorter hospital length of stay for neonates born to mothers receiving the interventions.[22]

First-line pharmacologic treatment

Opioid agonist therapy (OAT) using long-acting agonists is the standard of care for managing OUD during pregnancy. First-line OAT agents include methadone- and buprenorphine-based therapies, each with distinct biochemical and pharmacologic profiles.[6]

Methadone is a long-acting, full opioid agonist that exerts its effect by binding to opioid receptors in the central nervous system, thereby inhibiting ascending pain pathways.[23] Historically, methadone has been the treatment of choice for OUD during pregnancy.[6] It is important to note that pregnancy-related physiological changes accelerate methadone metabolism, necessitating increases in both dose and dosing frequency to maintain stable maternal-fetal opioid levels and prevent withdrawal.[24] Methadone is associated with several adverse effects. As a full agonist, methadone shares its side effect profile with other opioids. Such side effects include nausea, vomiting, gastroparesis, and constipation. Methadone also depresses central respiratory centres, increasing risk of respiratory failure.[23] Moreover, methadone interacts with several drug classes including antimicrobials and HIV medications, requiring close monitoring due to the common use of these drugs in the OUD patient population.[23] Lastly, there is dose-dependent QT prolongation effect that can increase the risk of maternal ventricular tachyarrhythmias (although this is rare). Despite these potential side effects, methadone treatment has been associated with a 33% reduction in overdose-related deaths.[25] Compared to other first-line OATs, methadone may be more appropriate for those with high tolerance, severe OUD, and/or treatment-refractory OUD.[6] Table 2 summarizes the management options for OUD in pregnancy.

Buprenorphine is a long-acting, high-affinity, partial opioid agonist. It has several advantages over methadone, including a wider therapeutic window and reduced risk of respiratory depression owing to its ceiling effect.[26] In the non-pregnant population, buprenorphine is associated with a significantly lower overdose risk compared to methadone (relative risk [RR] 4.25).[27] During pregnancy, the metabolism of buprenorphine is accelerated, requiring higher and more frequent dosing to manage withdrawal effectively.[28] Despite the availability of various buprenorphine formulations, few are used in pregnancy. The transdermal patch (Butrans) has little role in OUD management, given the low dosages administered and its lack of availability on provincial formularies. There is little evidence to support the use of the extended-release injectable form of buprenorphine (SUBLOCADE) in pregnancy, and there are concerns regarding this formulation which contains N-methyl-2-pyrrolidone (NMP), found to be teratogenic in mouse models.[6] In contrast, the combined formulation of buprenorphine with naloxone (Suboxone) has demonstrated favourable fetal outcomes in recent studies, leading Health Canada to lift its previous pregnancy use contraindication.[6] A 2020 systematic review and meta-analysis found that neonates born to individuals treated with buprenorphine were less likely to experience severe NOWS compared to those receiving full OAT.[29] Additionally, no significant differences were found in adverse fetal outcomes, such as low birth weight, preterm delivery, congenital anomalies, or stillbirth, between buprenorphine and methadone, supporting its use further.[29,30] Consequently, buprenorphine/naloxone is now accepted as first-line OAT, a position further reinforced by the Society of Obstetricians and Gynaecologists of Canada's 2023 Clinical Guidelines.[6] The potential benefits of buprenorphine for fetal health must be weighed against the increased risk and severity of withdrawal in pregnant individuals.[6,31] In non-pregnant populations, studies have shown that buprenorphine is associated with lower retention rates in treatment programs compared to methadone, although similar rates of abstinence have been observed among those who remain in treatment.

Alternative-line pharmacologic treatments

Naltrexone, an opioid receptor antagonist, is an alternative treatment option for OUD. However, it is rarely initiated de-novo in pregnancy because patients need to be abstinent off all opioids for 7 days prior to starting it. This can precipitate withdrawal, increasing risk of maternal morbidity and mortality.[32] Although available data are limited, there are no known adverse fetal or neonatal effects associated with the use of

Table 2. Management of opioid use disorder in pregnancy

Intervention Pharmacological	Drug class	Dosing	Additional comments
Buprenorphine Buprenorphine/naloxone (Suboxone)	Long-acting partial opioid receptor agonist	• Buprenorphine (oral)*: ◦ starting dose: 2 to 4 mg oral daily ◦ average dose: 16 mg oral daily • Suboxone (sublingual) induction*: ◦ Day 1: suboxone 2/0.5 it was closed ◦ Day 2: up to suboxone 16/4mg	• Partial agonist: ◦ less severe opioid like adverse event profile • more favourable fetal outcomes ◦ less severe NOWS ◦ less preterm labour ◦ less fetal bradycardia ◦ higher birth weight • higher withdrawal rates and more intense withdrawal symptoms • split doses required (up to 5-6/d) • safe for breastfeeding
Methadone	Long-acting partial opioid receptor agonist	• Starting dose*:10-30 mg oral daily • Average dose*: 80-120 mg oral daily	• full agonist ◦ more severe opioid like adverse event profile • less withdrawal rates and higher retention in programs • dose-dependent QTc increase • less favourable fetal outcomes ◦ more severe NOWS ◦ more PTL ◦ more fetal bradycardia ◦ lower birth weight • may require split dose • safe for breastfeeding
Slow-release oral morphine	Opioid	Patient specific	• used in conjunction with methadone • can breastfeed if neonate is opioid tolerant
Naltrexone	Opioid receptor antagonist	Monthly extended-release injection	• not initiated or routinely used in pregnancy • reasonable to consider continuing for stable patients upon pregnancy confirmation • unknown efficacy when compared to first-line opioid agonist therapy • no known adverse events with breastfeeding but limited data
Non-pharmacological			
Contingency management Motivational interviewing			• Some data suggesting the benefit of contingency management on decreasing neonatal hospitalization length

*Dosing based on non-pregnant, heroin-tolerant population
NOWS = Neonatal opioid withdrawal syndrome

naltrexone.[33] Additionally, there is lack of data comparing fetal outcomes between naltrexone and other first-line treatments for OUD. This is particularly important since injectable naltrexone is not available in Canada but is commonly used in other jurisdictions. For pregnant individuals who are stable on naltrexone, continued use may be considered to prevent destabilization.[6,34]

Emerging evidence from studies in the non-pregnant population suggests that slow-release oral morphine (SROM) may also be effective in reducing opioid cravings and could be particularly beneficial for individuals who experience inadequate withdrawal suppression or who are intolerant to traditional first-line treatments such as methadone or buprenorphine.[35,36] Earlier studies demonstrated comparable outcomes between SROM and methadone with regards to NOWS and fetal well-being.[37] Given the lack of robust comparative data with buprenorphine, SROM is currently considered an alternative treatment option for OUD in pregnancy and is typically only used as add-on therapy with methadone.[6,38]

Breastfeeding

Methadone, buprenorphine-based therapies, and naltrexone are all considered safe during breastfeeding. In fact, mothers who have remained stable on these treatments throughout pregnancy are generally encouraged to breastfeed.[39–41] Methadone transfers into breast milk in small amounts, approximately 2%–3% of the maternal dose.[42] Both buprenorphine and naltrexone are secreted at even lower levels into breast milk, at 1.4% and 0.9% of the maternal doses, respectively.[43,44] By contrast, the use of non-prescribed or illicit opioids during breastfeeding is strongly discouraged. While no specific studies have evaluated the safety of SROM in breastfeeding, evidence examining the use of morphine indicates that in opioid-tolerant neonates there should theoretically be no concerns about breastfeeding.

ALCOHOL USE DISORDER

Incidence and maternal-fetal outcomes

Alcohol use is highly prevalent among individuals of reproductive age in Canada, with significant implications for both maternal and fetal health. In 2019, it was estimated that 1 in 6 pregnancies were affected by alcohol use disorder (AUD) in Canada.[45] While most individuals with AUD during pregnancy report low-level alcohol consumption (defined as no more than 7 drinks per week, or no more than one binge drinking episode of more than 5 drinks in a sitting per week), moderate AUD affects approximately 1 in 25 pregnancies, and severe alcohol use is estimated to affect 1 in 100 pregnancies.[46] Current alcohol consumption recommendations are based primarily on cohort studies, which are susceptible to confounders such as socioeconomic status, genetics, pharmacokinetics, BMI, and co-consumption of other substances.[47] Consequently, the consensus on alcohol use in pregnancy by clinical guidelines is: "the less, the safer and none is best." For reference, the following amounts of alcoholic beverages are considered roughly equivalent in alcohol content and defined as a "standard" drink[48]:

- Beer/cider/cooler: 341 mL (12 oz) with 5% alcohol content
- Wine: 142 mL (5 oz) with 12% alcohol content
- Distilled alcohol: 43 mL (1.5 oz) with 40% alcohol content

The primary fetal risk associated with in-utero alcohol exposure is fetal alcohol spectrum disorder (FASD). FASD affects an estimated 2%–4% of Canadian youth.[47,49] In addition to FASD, alcohol consumption during pregnancy increases the risk of several adverse outcomes. These include increased risks of miscarriage (OR 1.19),[50] preterm labour (more likely with moderate alcohol consumption versus no consumption (OR 1.77),[51] and low birth weight (OR 1.25). Respiratory distress in neonates is also more likely with maternal AUD (OR 2.57).[52] Notably, for individuals consuming five or fewer drinks per week, each additional drink per week is linked to a 6% increase in miscarriage risk (OR 1.06).[51]

Maternal risks associated with alcohol use during pregnancy are extrapolated from the non-pregnant population and include increased risks of developing liver and biliary disease. In fact, AUD may represent 20%–50% of all cases of cirrhosis worldwide.[53] Additional risks include the development of acute and chronic pancreatitis, chronic hypertension, malnutrition (including thiamine deficiency), and dementia.[54] The effects of alcohol withdrawal during pregnancy remain inadequately studied, and data on fetal outcomes is limited. Studies suggest a potential association between alcohol withdrawal and adverse fetal outcomes, including preterm labour and IUGR. A retrospective study examining eight cases of severe alcohol withdrawal in pregnancy found high rates of intensive care unit admission (37.5%) and miscarriage or stillbirth (37.5%).[55] These complications are thought to result from dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis.[56] Mater-

nal complications of acute alcohol withdrawal are well documented and can be life-threatening. These include excitability, tachycardia, dysautonomia, hallucinations (tactile, auditory, or visual), confusion, and seizures (or delirium tremens).[57] The potential maternal and fetal risks underscore the importance of minimizing alcohol exposure during pregnancy and support that abstinence remains the safest recommendation.

Management

Treatment of low-level peripartum alcohol use: A non-pharmacologic approach

The primary treatment strategy for low-level peripartum alcohol use is non-pharmacologic, given that alcohol use is intricately linked with mental health and broader social determinants of health. Prenatal alcohol exposure is frequently associated with maternal experiences of violence, trauma, and depression, further complicating the management landscape.[58]

Interventions

Health care providers are strongly encouraged to screen for alcohol use during pregnancy, beginning with early prenatal visits through primary care providers. It is essential to identify both low-risk and problematic alcohol use. To facilitate open and honest disclosure, a safe, non-judgmental, and supportive environment must be established. Maternal willingness to disclose alcohol use can be influenced by factors such as fear of losing custody of a child, stigma, guilt, shame, and lack of social supports.[47,59] Several validated screening tools such as the T-ACE and AUDIT-C, are specifically adapted for use in pregnancy and can help identify individuals who may benefit from further intervention.[54] These tools guide health care providers in delivering "brief alcohol interventions," which are time-limited, evidence-based, use motivational interviewing techniques. These techniques focus on increasing awareness, advising reduction or elimination of consumption, and providing support for implementation.[47] Studies have shown that motivational interview-based interventions are more effective than traditional advice-giving methods in reducing alcohol use.[55] Links to these tools can be found in Table 1.

Timing and effectiveness of brief interventions

Brief interventions are most effective when implemented before conception.[60] Nevertheless, multicontact repeat sessions are strongly encouraged at any stage, including the post-partum period.[58] Furthermore, individuals who screen positive for alcohol use and benefit from brief interventions, should be referred to specialized treatment centres that can provide intensive care, ongoing support, guidance, and monitoring for alcohol use during pregnancy.[61]

Pharmacologic treatment

Pharmacologic interventions for alcohol use in pregnancy are primarily focused on managing withdrawal and supporting individuals with moderate to high alcohol exposure. There is paucity of data examining their use in pregnancy. Withdrawal management typically includes the use of benzodiazepines and thiamine, whereas naltrexone and acamprosate are used to promote abstinence. A summary of current pharmacologic treatment options for alcohol use in pregnancy, including withdrawal management protocols, is provided in Table 3.[6]

Breastfeeding

Midazolam, a short-acting benzodiazepine, is minimally excreted into breast milk (approximately 0.06% of maternal dose) and generally considered safe for use in breastfeeding mothers experiencing withdrawal symptoms or seizures.[62] Lorazepam and diazepam are the benzodiazepines of choice for treatment of alcohol withdrawal as their concentrations in breast milk are higher (1%–4% and 3%, respectively).[63,64] Breastfeeding is generally not recommended in unstable patients who require high doses of lorazepam or other benzodiazepines. In these cases, breastfeeding should be suspended, and alternative feeding methods should be used until the individual no longer requires high doses of benzodiazepines. If breastfeeding remains a priority for the mother, efforts to support milk production through pumping should be actively encouraged to maintain milk supply. Infants exposed to benzodiazepines should be closely monitored for potential side effects, including drowsiness, decreased feeding, and poor weight gain.[65] While most pharmacological agents used to promote abstinence in AUD are either understudied or contraindicated during breastfeeding, naltrexone is an exception, with data supporting its safety as extrapolated from the OUD population (see Table 3).

STIMULANT USE DISORDER

Incidence and maternal-fetal outcomes

Stimulant use during pregnancy is often underrecognized and includes both non-prescribed substances,

Table 3. Management of alcohol use disorder in pregnancy

Drug	Indication	Additional comments
Naltrexone (opioid receptor antagonist; reduces cravings)	Relapse prevention (moderate-severe AUD)	• Limited data for use in pregnancy • Emerging safety data from OUD population is reassuring but should only be prescribed if benefits outweigh risks • Safe in breastfeeding as it is minimally excreted in breast milk
Acamprosate (GABA agonist; reduces cravings)	Relapse prevention (moderate-severe AUD)	• Limited overall data for use in pregnancy but primary data suggests safety during gestation • Prescribed as benefits outweigh risks • Not studied in breastfeeding
Disulfiram (aldehyde dehydrogenase inhibitor)	Relapse prevention (moderate-severe AUD)	• Teratogenic in first trimester • Induces adverse maternal reaction following alcohol ingestion • Risk of severe maternal hypertension and autonomic dysregulation when used with alcohol and pregnancy • Not studied in breastfeeding
Topiramate (mechanism unknown; reduces drinking)	Relapse prevention (moderate-severe AUD)	• Should be avoided in pregnancy (risk of cleft lip/palate and small for gestational age) • Excreted in breast milk • No high-quality safety data for breastfeeding but has been used when other strategies have failed
Gabapentin (dopamine release inhibitor)	Relapse prevention (moderate-severe AUD)	• Used as an alternative-line treatment • No increased risk of malformations but reports of IUGR and developmental delay • Excreted in breast milk • No high-quality safety data for breastfeeding but has been used when other strategies have failed
Benzodiazepines	Withdrawal management	• Diazepam is the agent of choice for the treatment prevention of withdrawal seizures • If delivery is imminent consider midazolam instead (short-acting benzodiazepine) • Safe for short-term use but newborns should be monitored for withdrawal if used within days of delivery • Short-acting benzodiazepines are minimally excreted in breast milk, but breastfeeding is not recommended for unstable patients requiring high doses of benzodiazepines
Thiamine (vitamin B1)	Withdrawal management	• Increase thiamine needs in pregnancy • No known adverse effects of high-level parenteral thiamine • Dietary supplementation of thiamine is recommended in breastfeeding women with history of alcohol withdrawal • Safe for breastfeeding

AUD = Alcohol use disorder; OUD = Opioid use disorder; IUGR = Intrauterine growth restriction

such as cocaine and methamphetamine, as well as prescription stimulants.[66] While data on the exact prevalence of stimulant use in pregnancy is limited, there has been a notable increase in the use of cocaine among Canadians aged 20–24 years. Use rose three-fold from 2013 to 2019, with an estimated prevalence of 9% in this age group.[67] A similar upward trend has been observed for other non-prescription and pre-

scription stimulants, with the latter affecting 5–6 out of every 100 Canadians in the same age range.[67]

Cocaine is derived from the South American coca bush. When snorted, it produces a dramatic and prolonged dopamine effect in the limbic system and cerebral cortex. Methamphetamine is the methylated derivative of dextroamphetamine. It is a central nervous system stimulant that causes intense euphoria when snorted, smoked, or injected.[66] Maternal use of non-prescribed stimulants is associated with a range of adverse outcomes. Case series have demonstrated associations between maternal cocaine use and hypertension, myocardial infarction, ventricular tachyarrhythmias, renal failure, hepatic rupture, stroke, and maternal death.[66] Methamphetamine use during pregnancy has a similar risk profile, with the added concern of severe maternal dental disease.[68]

From a fetal perspective, cocaine use during pregnancy is associated with a significantly increased risk of preterm birth, IUGR, preterm premature rupture of membranes (PPROM), and placental infarction.[69] Pregnant individuals with active cocaine use are also nearly three times more likely to experience placental abruption (OR 2.79) and more than twice as likely to develop eclampsia (OR 2.20).[70] Methamphetamine use is linked to several adverse outcomes, including intrauterine fetal death (IUFD) and placental abruption (OR 5.1 and 5.5, respectively).[71]

Data on maternal and fetal outcomes associated with the misuse of prescription stimulants during pregnancy is limited and controversial. Most avail-

Table 4. Management of stimulant use disorder in pregnancy

Intervention	Indication	Dosing	Additional comments
Pharmacological			
Mirtazapine	Methamphetamine use	Mirtazapine 30-40 mg oral daily	• Data are extrapolated from study examining cisgender men and transgender women who have sex with men • No significant adverse events in pregnancy • Safe in breastfeeding
Injectable long-acting naltrexone with daily bupropion	Methamphetamine use	Naltrexone 380 mg SC monthly and bupropion 450 mg oral daily not available in Canada	• Bupropion deemed relatively safe in 2017 SR • Long-acting naltrexone is difficult to obtain in Canada special access could be granted through provincial programs, but the cost needs to be covered by the patient • No data in breastfeeding
Non-pharmacological			
Contingency management	All stimulant use		• Robust data showing efficacy and pregnancy • Difficult to implement given barriers to care in our current health care system
Matrix model	All stimulant use		• Some evidence supporting efficacy
Cognitive behavioural therapy	All stimulant use		• Some evidence supporting efficacy
12-step facilitation	All stimulant use		• Some evidence supporting efficacy

SC = Subcutaneous; SR = Systematic review

able information is derived from studies involving individuals treated for attention-deficit hyperactivity disorder (ADHD).[66] In this population, several cohort studies suggest that exposures to prescribed methylphenidate and amphetamine are not associated with increased risk of congenital anomalies.[72,73] In another population-based cohort study, women exposed to prescription stimulants developed increased risk of preeclampsia (RR 1.26) and delivering small for gestational age neonates (RR 1.37).[74] Several cohort studies from the United States have reported a modest increase in the risks of preeclampsia, placental abruption, and preterm labour among pregnant individuals using prescription stimulants; however, these findings have not been replicated across other studies.

Management

There are currently no approved pharmacotherapies for the treatment of stimulant use disorder during pregnancy. Management is primarily non-pharmacologic with contingency management showing the most promise in non-pregnant individuals.[24] Implementing a contingency management approach in Canada's health care system is challenging due to resource limitations, financial constraints, lack of evidence-based standardization for pregnancy care, and difficulties ensuring long-term follow-up. Other non-pharmacologic interventions in pregnancy that are promising include the Matrix Model, cognitive behavioural therapy, and 12-step facilitation.[19]

Mirtazapine has been shown to reduce stimulant use in cis-gender men and transgender women who have sex with men in a recent study.[75] Given its safety profile, mirtazapine is currently the agent of choice to treat stimulant use disorder in pregnancy. The use of topiramate and long-acting amphetamines has not demonstrated effectiveness, even in non-pregnant populations. Studies on the safety of antiepileptics during pregnancy have shown that topiramate is linked to a higher risk of major congenital malformations compared to controls (risk ratio 4.01).[76] While several studies support the use of combination injectable extended-release naltrexone and daily bupropion for managing methamphetamine use,[77] extended-release naltrexone is not available in Canada without authorization through Health Canada's Special Access Program. Furthermore, the high cost of the medication is often prohibitive.[6] Table 4 summarizes the management options for stimulant use disorder in pregnancy.

Breastfeeding

Mirtazapine is excreted in breast milk (1%–1.5% of maternal dose). Safety data in breastfeeding is based on case reports and case series, which did not observe feeding or sleeping difficulties in exposed babies.[78] Long-acting amphetamines are excreted in breast milk and their use during breastfeeding should be carefully weighed against the potential risks of therapy discontinuation. An older study examining the breast milk of a woman treated for narcolepsy with racemic amphetamine recommended a daily threshold of 20 mg as this amount did not show evidence of adverse fetal event up to 2 years of age.[79] A more recent case series suggested that maternal dosing of methylphenidate of up to 80 mg daily was not associated with adverse fetal events.[80] In contrast, naltrexone-based therapies are considered safe and compatible with breastfeeding.

CONCLUSION

Substance use disorders involving opioids, alcohol and stimulants during pregnancy are highly prevalent and pose significant risks to maternal and fetal health. Effective management requires a comprehensive, interdisciplinary approach, with health care providers across specialties equipped to address a myriad of challenges safely. Non-pharmacologic interventions, such as behavioral therapies, contingency management, motivational interviewing, and psychosocial support, are central to managing substance use disorders during pregnancy and the post-partum period. Pharmacologic options are limited and often understudied in the pregnant and post-partum populations. Further research is required to better understand the prevalence of use disorders, assess the safety and efficacy of pharmacologic treatments, and ultimately enhance care for these vulnerable groups.

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ETHICS APPROVAL

N/A

INFORMED CONSENT

N/A

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

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All data will not be made publicly available. Researchers who require access to the study data can contact the corresponding author for further information.

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