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MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.9 Recommendations for the Treatment of Opioid Use Disorder in Pregnancy

GENERAL CONSIDERATIONS

This chapter aims to empower opioid agonist therapy (OAT) providers to support individuals throughout pregnancy and postpartum with confidence and compassion, while utilizing evidence-based best practices.

The literature reviewed in generating these recommendations include sources dated after 1990 from Medline, Pubmed, The Cochrane Library with word searches including: opioid, morphine, heroin, methadone, Suboxone and pregnancy, postpartum, fetus, mothers and dependence, misuse, addiction and use disorder. Guidelines from the Society of Obstetricians and Gynaecologists, American Conference of Obstetricians and Gynecologists, the Royal College of Obstetricians and Gynecologists, Association of Ontario Midwives and Nursing and Midwifery Council (UK) were also searched for recommendations.

Principles of Truth and Reconciliation, patient-centered and trauma-informed care, inter-professionalism, and harm reduction are endorsed in this chapter. The parent-infant dyad is inherently valued and custodial parenting is promoted, when it is the goal of the patient. Not all pregnant individuals identify as female, so most language is intended to be gender-neutral for inclusivity. However, there are elements of lived experience that are specifically gendered, and these will be addressed accordingly.

Substance-involved pregnancy is high risk for social instability, violent exposures, postpartum depression, suicide, and unintended overdose, with a disproportionate and growing burden of maternal morbidity and mortality. Infants born from these pregnancies have a high rate of prematurity, neonatal intensive care unit (NICU) admission, and long-term neurobehavioral sequelae. Stabilizing opioid use disorder (OUD) in pregnancy reduces the likelihood of these negative outcomes, while also reducing the need to rely on emergency services and minimizing NICU admission days. Effective treatment simultaneously serves to enhance patients' experience of dignified care and reduces cost-burdens to the system.

SUMMARY OF KEY RECOMMENDATIONS

The following key recommendations listed here are discussed throughout this chapter:

1) All individuals supported on OAT who are of reproductive age should be offered the opportunity for **effective contraceptive and preconception counseling**.

2) If pregnancy is discovered after OAT induction, patients should be reassured that their **maintenance therapy is gold standard care** for pregnant persons with OUD, and that there is no need to dose-restrict due to pregnancy.

3) For OAT induction during pregnancy, evidence is still emerging. While methadone has a more extensive lineage in the literature, **buprenorphine/naloxone treatment may be considered as a first-line agent in pregnancy**. Micro-dosing with buprenorphine/naloxone may be considered with close supervision over a traditional start to avoid withdrawal.

4) Cycles of use and withdrawal impose vasoconstriction and severe fluid shifts in pregnancy. This compromises placental perfusion, and **patients should be educated about the importance of avoiding withdrawal in pregnancy**. They should also be reassured that their prescribers/OAT care teams will treat these presentations.

5) Community based opioid weaning should be limited to highly motivated patients who, after thorough risk-benefit discussion, decline OAT therapy. **Cessation, even if closely supervised, is *extremely high risk*** for relapse to unprescribed opioids, maternal overdose, and placental malperfusion imposed by the requisite withdrawal. This approach has also not been proven to improve newborn outcomes.

6) Opioid use is often a barrier to presenting for maternity care. Providers should encourage the **use of all available community resources and make prompt referrals to maternity care** providers who are familiar with OAT. This may include, and is often enhanced by, a shared-care approach with outreach nursing, obstetricians, midwives, and allied health.

7) **Smoking cessation counselling should be considered as a first-line intervention** for pregnant smokers, given the synergistic harms of smoking and opioid use in pregnancy. To date there is sufficient safety evidence to also recommend both bupropion and nicotine replacement therapy (NRT) in pregnancy.

8) Symptoms common in pregnancy, such as nausea and vomiting, can be distressing and act as provocative triggers for relapse given their overlap with opioid withdrawal symptoms. **Antiemetics should be easily accessible and consider interval EKG studies to assess QT intervals** for patients on OAT (particularly methadone) who require other QT-prolonging medication(s) for symptom control. Typically, non-sedating antiemetics are used first line. However, for severe symptoms a regimen utilizing more than one agent may be required.

9) OUD predisposes patients to hyperalgesia so **consultation with anesthesia prior to delivery should be considered**. OAT does not provide effective analgesia in labour.

10) The approach to **infant nutrition should be weighed on an individual basis**. OAT is not a contraindication to breastfeeding which is, in turn, associated with reduced neonatal opioid withdrawal scores and increased parent-infant bonding.

11) Opioid-involved pregnancies are high risk for postpartum depression and suicide. **Screening for depression should occur at each trimester and postpartum follow-up should be enhanced**. Patients should be screened by a care provider within two weeks of delivery. Neither pregnancy nor breastfeeding are contraindications to antidepressant therapy.

12) Intimate partner violence and relationship discord are highly correlated with postpartum relapse and overdose. **Screening for relationship instability should occur in each trimester**, with safety planning as indicated.

13) OAT is not a reflection of parenting capacity. Patients should be offered support through local community programs for prenatal and/or parenting classes that are culturally safe and aligned with parenting values. Involvement of Child Protection Services (CPS) should be limited to documented unsafe behavior with infants/children already in the home. **OAT in pregnancy is not an indication to report**.

14) Infant apprehension is an important risk factor for maternal mortality in the opioid-involved pregnancy. If CPS are asked to assess for apprehension, **wrap around supports are urgently indicated for maternal welfare**.

15) Tapering OAT within the first postpartum year is highly correlated with relapse and unintended overdose. Patients should be advised to titrate the dose to effect as they would non-pregnant, and encouraged to **postpone plans to taper OAT until their newborn is over one year of age**.

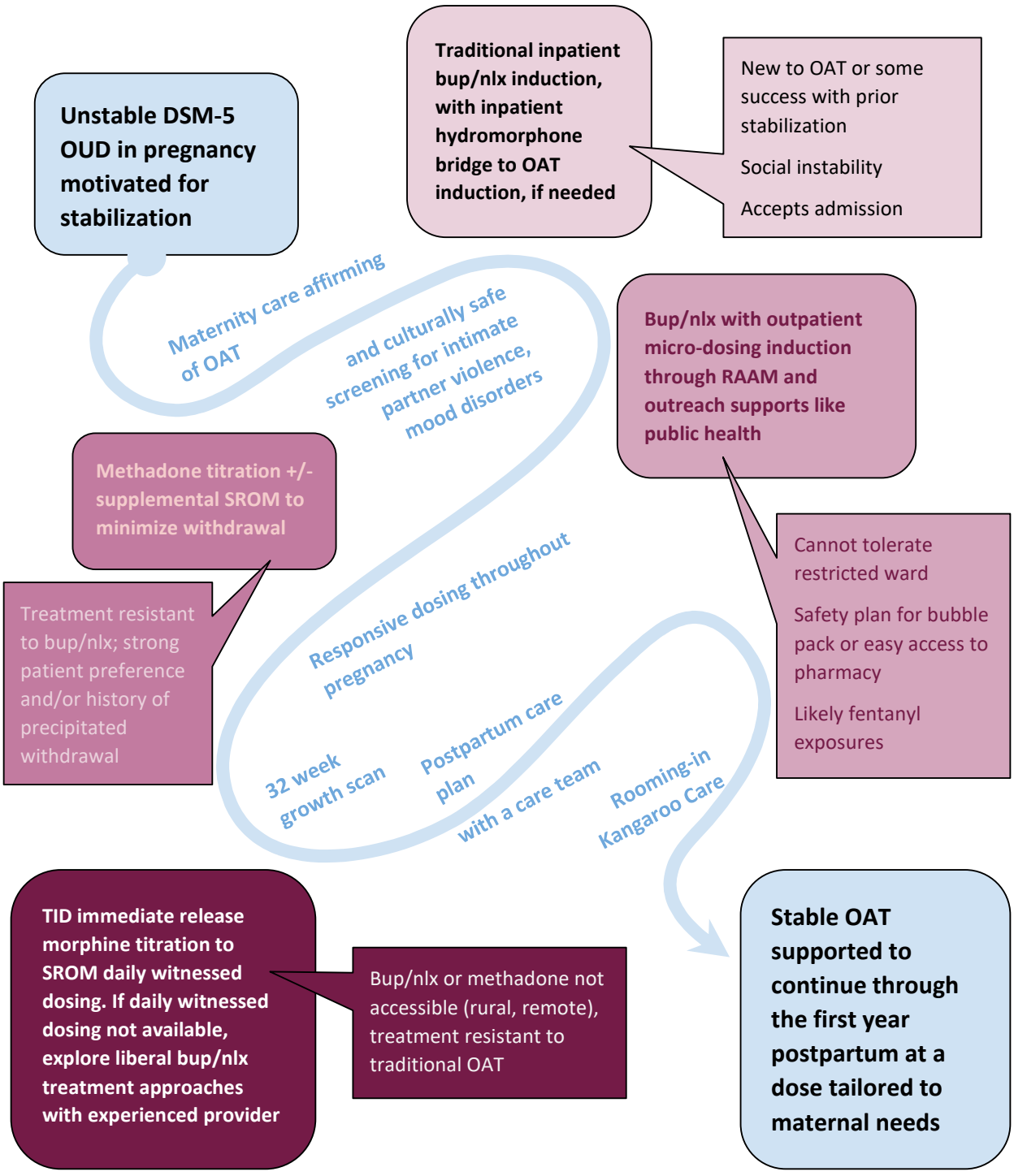


Figure 1: More Than One Path to Stability

OAT in pregnancy requires a backbone of dignified, trauma-informed, and culturally safe care with a longitudinal view into the first year postpartum. Dosing is often gradually titrated upwards over time, especially in the third trimester. This approach ensures treatment addresses changing maternal needs. Four induction models are outlined here, including a description of patient features that lend themselves to each modality.

SPECIFIC CONSIDERATIONS

Receptor sensitivity, metabolic rates, drug-drug interaction, and vulnerability to QT-prolongation are different between male and female patients on OAT.[1] This results in a more rapid progression from first opioid use to the development of OUD in women. Women also experience higher rates of fatal overdose (especially with co-ingestion of benzodiazepines), and increased lethality from cardiac effects of opioid use.

These vulnerabilities are further modified by pregnancy, during which opioid metabolism is increased and harmful maternal outcomes are more frequent, such as unintended overdose and violent exposures.[2] The hormonal milieu exacerbates mental health conditions and can lead to depression, psychosis, and suicide. This extends into the psychosocial world of pregnant persons on OAT. Intersectional theory considers where overlapping marginalization can compound barriers to care and exacerbate negative outcomes. For the opioid-involved pregnancy this is particularly evident amongst Indigenous populations. Social expectations, implicit bias, and systematic racism collide with impact to the maternal-newborn dyad in the context of neonatal care.

However, pregnancy is also a potent motivator for change, and can be a powerful opportunity for recovery and care engagement. Illuminating these differences in pregnancy and adapting OAT to accommodate these needs can provide empowered, nuanced care. OAT care guided by the values and principles described below can cultivate this engagement and empowerment.

Principles of Truth & Reconciliation

The first Call to Action of the Truth and Reconciliation Commission (TRC) is to honour and preserve the family unit and community ties of Indigenous persons. This Call identifies a history of cultural bias and inequity that has been inherent in the work of Canada's CPS agencies, and challenges Canadians to seek healing within and between communities. Patients who have been supported on OAT during pregnancy have had a disproportionate and sometimes unindicated involvement with CPS, exacerbating these racialized inequities.

OAT providers should be aware of the risk of infant apprehension that is linked to substance use disorders, and the **deep sense of anxiety patients feel about losing their child** should they seek out and continue with OAT care during pregnancy and postpartum. Since OAT is the standard of care for the treatment of OUD in pregnancy, this is an important opportunity for advocacy.

Patient-Centred Care

"Patient-centered care puts patients at the forefront of their health and care, ensures they retain control over their own choices, helps them make informed decisions, and supports a partnership between individuals, families, and health care services providers."[3]

This is actionable through dignity-preservation, information sharing, participation, and collaboration between the patient and their providers. In maternity care, there is still outdated language such as physicians "letting" patients labour, deliver vaginally, and even continue with OAT. It is important to invite patients to identify their goals of care and then align with them as safely as possible.

Cultivating a care plan together, not only for pregnancy but also for the first year postpartum, keeps patient values at the centre of the therapeutic alliance.

Trauma-Informed Care

Traumatic life experiences are those which fundamentally have an element of terror, isolation and helplessness.[4] The features of the event itself are not an important defining factor, but rather how they are experienced and processed by the survivor. "[Trauma] is not a thing that you have. This is a process that expresses your life experience."[5] Subsequent experiences that literally or symbolically recapitulate the traumatic experience can trigger post-traumatic symptoms and create powerful barriers to care.

Many of the events of childbearing are high risk for unintended re-traumatization. For example, intimate exams, overwhelming physical symptoms with limited ability to suppress them, and pain that can mimic opioid withdrawal. These experiences can destabilize an OUD in remission or decompensate mental health. Seeking opportunities to maximize safety, therapeutic relationships, and agency are meaningful antidotes to the features of trauma.

Inter-Professionalism

Opioid-involved pregnancy represents a clinical situation that arises from a multifaceted pathogenesis. Elements of childhood adversity, social inequity, genetic endowment, and familial coping all contribute to the development of addiction. Pregnancy is a collision of changing physiology, social roles, and personal identity. Both have vulnerability to complex infections, mental health instability, and intimate partner violence. Together these comorbidities can be significant.

One patient may require support from Addiction Medicine, Cardiology, Obstetrics, Social Work, Endocrinology, Psychiatry, Public Health, and Neonatology, all before the baby is even born. Medical silos result in care-redundancies, lack of continuity, and missed treatment opportunities, all of which exacerbate negative outcomes. **Increasing timely, reciprocal communication between providers, including case conferencing with patients leading the discussion, can help optimize care-efficiencies and improve outcomes**.

Harm Reduction

The recovery journey is a spectrum of goals and experiences that range from frequent, high-dose, unregulated use to absolute abstinence with a wide variety of use- and care-engagement along the way.

For some patients, their definition of recovery may not include abstinence; for others, anything short is considered failure. Meeting patients where they are at, on *their path* to the recovery *they value*, is a requisite first step in harm reduction.

Identifying behaviors which increase the risks of overdose, complex infection, violent exposures, criminal engagement, and/or housing and food insecurity can illuminate opportunities to intervene to minimize these harms.

In the setting of pregnancy, harm reduction also considers the developmental impact of opioid exposure to the fetus, the perfusion effects of use or withdrawal upon the placenta, congenital infection secondary to intravenous use, and the interplay between substance use and preeclampsia or gestational diabetes. **OAT providers can collaborate with maternity care professionals to optimize harm reduction together as it aligns with patient care goals**.

1) All individuals supported on OAT who are of reproductive age should be offered the opportunity for effective contraceptive and preconception counseling.

OAT providers can provide essential counselling to reduce the risk of blood borne infections for their patient, their patient's sex/use partners, and their unborn children. By supporting reproductive planning, OAT providers can promote social stability and optimize parenting outcomes. OAT itself improves obstetrical outcomes for both maternal and newborn benefit. While ongoing study is needed to define long-term neurobehavioral effects of fetal OAT exposure, current evidence supports long-acting opioids as decidedly superior to unregulated use in pregnancy. This counsel is meaningful for expectant patients, those considering future fertility, and anyone who might be involved with an unplanned pregnancy.

Infection Risk Reduction

The frequency of Sexually Transmitted and Blood-Borne Infection (STBBI) that follows unregulated opioid use impacts males and females equally. The implications of subsequent sexual transmission should be addressed by care providers. Risk is not limited to intravenous drug use (IVDU). Unregulated oral opioid use is associated with increased unprotected sex, survival sex trade, and sexual violence leading to increased infection rates.[6]

OAT providers must offer comprehensive screening for STBBIs to all patients with OUD. Initial and intermittent STBBI screening, including treatment referrals as appropriate, form an important part of ongoing OAT care. This can occur periodically after intake, based on ongoing risk assessment.

Patients at significant and ongoing risk of infection should be offered STBBI screening every 6 to 12 months. Repeat testing may be customized based on individual risk factors. The chapter on HIV & Hepatitis C Prevention, Screening, & Management in OUD provides further guidance, along with the recommendations below.

Patients with a diagnosis of STBBI should be provided with barrier prophylaxis (some coverage providers may honour a prescription for condoms) and education about the risk of congenital transmission/harms and the impact of pregnancy on treatment options. Traditionally, these discussions are limited to female-presenting patients who are already pregnant, which negates male agency in transmission and treatment, and misses an essential audience for public health education.

Online resources (CATIE.ca)[7] can help facilitate these discussions, and shared-care models may induce obstetrical referral for more in-depth counselling.

- **Human Immunodeficiency Virus (HIV)**: Manitoba has the second highest rate of HIV infection in Canada,[8] a growing statistic in step with the opioid crisis in Western Canada. Risk of acquisition is gendered, with male HIV primarily associated with men who have sex with men (MSM), with about 11% linked to IVDU. Female infection is a consequence of heterosexual sex (63%) and IVDU (27%).

  The risk of vertical transmission of HIV is about 45% in absence of treatment[9], which can be reduced to 2% with effective antiretroviral therapy (ART) and appropriate delivery planning. Regular screening, prompt referral to wrap-around HIV care programs, and continued efforts to de-stigmatize HIV are all effective harm reduction strategies. Administration of ART in the same clinic/pharmacy as OAT improves medical adherence.[10]

- **Hepatitis C Virus (HCV)**: 80% of HCV infection in Canada is secondary to IVDU[11] with a 52:48 distribution between the sexes (F:M), and significant overrepresentation among Indigenous communities.[12] The risk of transmission to a fetus can be as high as 38% particularly if the maternal viral load is >1 million IU/L, if alcohol use is concurrent to infection, if HIV is comorbid, and obstetrical interventions are used which increase fetal exposure to maternal blood (scalp clips/sampling, vacuum extraction, prolonged rupture of membranes).[13]

  Male patients can protect future offspring with timely treatment and barrier contraceptives to avoid exposing their sex partner(s). Female patients should use effective contraception to prevent a pregnancy until their HCV treatment is complete as both pregnancy and breastfeeding are contraindications to HCV antiviral therapy. Other harm reduction initiatives include alcohol abstinence, at least until the conclusion of antiviral therapy, and comprehensive treatment of HIV. Repeat testing in the third trimester is indicated, given the 2-3 month interval for seroconversion with new infection.[14]

- **Hepatitis B Virus (HBV)**: HBV affects approximately 200,000 Canadians at present, with a higher risk for fulminant liver disease than HCV.[15] Alcohol use disorder, IVDU, and comorbid HIV/HCV are risk factors for acute HBV infection.

Less obviously, major mental illness is an independent risk factor for HBV, likely a consequence of maladaptive coping with high-risk behaviours.

Opportunistic vaccination is the most important harm reduction intervention for the OAT provider,[16] and is safe during pregnancy. High maternal viremia (>3.8 × 10^8 copies/mL) has an odds ratio of 147 for fetal co-infection.[17] Tenofovir and Telbivudine are pregnancy class B drugs[18] and can prevent vertical transmission when administered in late pregnancy.[19]

- **Syphilis**: In 2019 a syphilis outbreak was announced in Alberta, following a 10-fold increase in this infection across the prairies.[20] What was considered an eradicated disease has returned to rates not seen since 1948. This is largely attributed to increased laxity in barrier prophylaxis use following the advent of ART, pre- and post-exposure prophylaxis, and the perceived survivability of HIV.[21]

  Congenital syphilis is now, likewise, on the rise, with social determinants such as poverty, unstable housing, substance use, and trauma contributing to both increased infectious exposure and decreased prenatal care.[22]

  An important gap in congenital syphilis prevention is the male partner. Minimal screening and refusal of treatment increase maternal re-exposure despite prenatal care and maternal treatment. Counselling all patients with syphilis about the risks to an unborn child (miscarriage, still birth, blindness, deafness, and/or bone deformities)[23] may help motivate male and female carriers alike to complete treatment.[24]

CLINICAL PEARL: WHY WON'T MY PATIENT ACCEPT TREATMENT?

Acting against medical advice (AMA) can threaten the therapeutic alliance between providers and their patients. For clinicians, the linear equation of Diagnosis + Treatment = Health seems obvious, and refusal of care can be experienced as a personal rejection.

Instead, this care-disengagement can be viewed through a trauma-informed lens. For marginalized patients "the traumatogenic effects of oppression that are not necessarily overtly violent or threatening to bodily well-being [can] do violence to the soul and spirit"[25] and may not only impair trust in the medical system, but also can erode self-preservation.

Recognizing AMA as a potential manifestation of trauma or colonization, rather than simply a difference of opinion can motivate more nuanced discourse. An assumption that patients make their decisions for important reasons helps preserve the relationship.

Trust is a therapeutic agent and measurably improves obstetrical outcomes.[26]

Social Instability Reduction

Patients who are new to OAT are embarking on a journey of recovery that may be complicated by untreated mental illness, trauma, poverty, violent exposures, criminal engagement, and homelessness. All of these factors impart an increased burden of morbidity and mortality.[27]

Approximately 65% of pregnant persons with OUD have co-occurring psychiatric conditions such as anxiety, depression and suicidal ideation.[28] All of these social comorbidities worsen obstetrical outcomes, contributing to prematurity, low birth weight, and increased pregnancy loss.[29] Similarly, pregnancy with its complement of mental health vulnerabilities, can destabilize one's recovery. While pregnancy is an important motivation for change, the **postpartum period is particularly high-risk for relapse and unintended overdose** (see **Maternal Benefits of OAT** below).

Exploring patient goals to start or grow their family can lead to more strategic planning for the OAT supported patient. Establishing psychosocial stability prior to pregnancy is associated with a greater likelihood of custodial parenting, term delivery, and a lower-risk postpartum interval.[30]

Advocating for long-acting reversible contraception (LARC) as the most efficacious option, hormone therapy for persons with irregular or symptomatic menses (co-administered with daily-dosing), and barrier prophylaxis for all can be a useful starting place. Depot injection contraception may be triggering for patients recovering from IVDU, but is otherwise very effective especially for those with chronic pelvic pain. It is important to remember, however, that marginalized populations may have negative experiences with coercive contraception planning, and **great care must be taken to champion autonomy**.[31]

- **Maternal Harms of Disordered Opioid Use**: In Canada, opioid overdose rates have increased by 50% over the past decade, now surpassing motor vehicle accidents as a leading cause of death among young Canadians.[32] [33] In the general population, unregulated opioid use is associated with sex trade, HIV and HCV infection, violent exposures, incarceration and socioeconomic marginalization.[34] During pregnancy, the consequences are grave with a 3.6-fold increase in cardiac arrest and a 4.6 times increase in mortality rates.

  Prenatal care is significantly limited, delaying diagnosis for complex infections such as cellulitis and endocarditis with a consequent increased risk for sepsis, ICU admission, and mortality. A study between Canada and Britain revealed that the risks of opioid-involved pregnancy had a long-reaching effect. Using neonatal opioid withdrawal syndrome (NOWS) as a surrogate for severe, active OUD in pregnancy, they identified a mortality rate of 1:20 over the subsequent 10 years.[35]

- **Fetal Harms of Opioid Exposure**: Fetal opioid exposure in pregnancy has grown by 16-fold over the past decade, and is associated with fetal growth restriction, low birth weight, preterm birth, and intrapartum fetal distress.[36] There is also growing evidence that associates first trimester opioid exposure with fetal cardiac and neural tube defects and gastroschisis[37] [38] though this is not consistent throughout the literature.[39] [40]

  Withdrawal itself compromises placental perfusion, resulting in intrauterine growth restriction (IUGR). The risk of placental abruption increases by about 2.4 times, which increases both maternal and neonatal ICU admissions and demise. Neurodevelopment is compromised, with reduced brain volumes than unexposed peers.[41]

- **Maternal Benefits of OAT**: The opioid crisis has driven more research in the area of opioid-exposed pregnancies. The majority of literature focuses on the fetal harms of opioid exposure in pregnancy. Advocating for maternal needs and best interests is of particular importance for marginalized populations.

  In pregnancy OAT:

  - Reduces relapse[42]
  - Reduces HCV/HIV[43] transmission
  - Reduces risk-taking activities[44]
  - Reduces overdose[45]
  - Increases prenatal care[46]
  - Increases custodial parentage[47]

- **Fetal Benefits of OAT**: Fetal impacts of opioid-involved pregnancy are still being explored. Prenatal exposure modifies several neurobehavioral systems in the newborn including sensory integration, state and motor/tone control, and autonomic activation. This manifests in hyper-stimulation response, resistance to being soothed, tremor, difficulty sustaining latch, and suppressed appetite. These are measured in feeding and sleeping behaviours, social and emotional interactions (neonatal abstinence syndrome [NAS] and NOWS scores), and often result in failure to thrive.[48] Concurrent nicotine, benzodiazepine, and antidepressant exposures may worsen these presentations.[49]

  Studies which contrast OAT-supported pregnancy with unregulated opioid-involved pregnancy, however, show reproducible fetal benefits. In the fetal environment, OAT:

  - Decreases miscarriage, stillbirth, and neonatal demise[50]
  - Improves birth weight[51]
  - Improves neurological development[52]
  - Decreases prematurity[47]
  - Reduces NOWS[53] [54]

2) If pregnancy is discovered after OAT induction, patients should be reassured that their opioid agonist therapy is gold standard care for pregnant persons with OUD, and that there is no need to dose-restrict due to pregnancy. In fact, physiological changes of pregnancy can necessitate a dose-increase.

Obstetrical advisory bodies in Canada, the US, and the UK all identify OAT as the **gold standard** for opioid-involved pregnancies[55,56,57] yet pregnant patients fear discrimination in the maternity care environment if they continue their OAT. This perceived stigma becomes a barrier to OAT adherence[58] and can limit participation in prenatal care, which is the single-most important protective factor for a positive obstetrical outcome.

OAT providers can validate that prioritizing maternal health naturally prioritizes fetal well-being and that maternity care providers and child protective agencies alike increasingly look favorably upon OAT engagement.[59]

- **Avoid dose-restriction**: Effective, adequately dosed OAT suppresses withdrawal and cravings for 24 hours, and prevents or significantly reduces unregulated use. This care goal is unchanged by pregnancy. Patient perception is often that dose-reduction will minimize fetal harms. Pregnant persons thus often endure increasingly severe withdrawal symptoms in the intent to spare their unborn child.

  OAT tapers in pregnancy are associated with a dramatic relapse rate. For those who completely wean, the relapse rate is 96%.[60] Fetal exposure to withdrawal is associated with the deleterious effects of unregulated use such as prematurity and growth restriction.[61]

- **Anticipate dose increase in third trimester**: Methadone metabolism, particularly, changes over the course of pregnancy, frequently requiring a need to increase the OAT dose, typically starting around 28-weeks gestation.[62] [63] Patients should be counselled ahead of time to anticipate this shift, and to interpret it as a physiological interaction with pregnancy, not a sign of failed recovery.

  Pregnant patients should be seen more frequently, starting at 28 weeks, to ensure regular evaluation of dose adequacy and to facilitate timely dose adjustments. Specifically, in the absence of other significant complications, these patients should be seen **every 2 weeks starting at 28 weeks** gestation, and **weekly starting at 34 weeks** gestation. A blended model of in-person and virtual care appointments may be offered to decrease the travel and financial burden of regular assessments during the third trimester. Video visits are preferable when assessing withdrawal, but may not always be practical or accessible for the patient. Pregnant patients on methadone especially may require *multiple* small dose increases over the course of the third trimester.

Conversely, there is a risk for somnolence with increased potency of OAT following the dramatic fluid shifts of delivery and subsequent volume contraction. **Postpartum patients should be counselled regarding, and monitored for, excess sedation in the postpartum period**. Patients must be advised how to reach their OAT provider if urgent dose reductions are required.

- **Consider increased dosing frequency (split dosing)**: New studies suggest that physiologic changes of pregnancy alter the half-life of buprenorphine, with less durable effects of OAT to suppress withdrawal symptoms.[64] This may be a consequence of plasma expansion, increased eGFR, or both, but serum concentrations can drop below a therapeutic threshold after 8 hours, particularly if the daily dose is less than 12 mg. This effect is more pronounced in the second trimester when plasma volume peaks.

  Consideration of divided doses may be more beneficial in pregnancy than just a dose-increase. A 50/50 split is *not* usually required to address withdrawal associated with altered metabolism. A much smaller evening dose is often sufficient to address withdrawal symptoms not alleviated by further increases to once daily dosing.

  Similarly, methadone metabolism is increased in pregnancy and patients may likewise benefit from divided doses. This effect is typically more pronounced toward the latter part of the third trimester. Typically, when withdrawal is reported at the end of the dosing interval, the **once daily methadone dose is optimized first**. However, if further AM dose increases cause sedation at the serum peak without adequately suppressing withdrawal towards the end of the dosing interval, consideration may be given to adding a small PM dose of methadone to eliminate withdrawal before the next day's dose.

  Patient stability needs to be carefully considered when considering divided doses in pregnancy, including the patient's ability to safely store take-home doses (carries) of methadone or buprenorphine. These considerations, including an overall risk-benefit analysis, must be documented when authorizing evening carries in pregnant patients who do not routinely qualify for take-home doses.

  Inexperienced providers or those uncertain of the safety/appropriateness of take-home doses in pregnancy are strongly encouraged to seek guidance from an experienced OAT provider who frequently cares for pregnant patients. See the Ongoing Care chapter, specifically the section on split-dosing for further recommendations.

3) FOR OAT INDUCTION DURING PREGNANCY, EVIDENCE IS STILL EMERGING. WHILE METHADONE HAS A MORE EXTENSIVE LINEAGE IN THE LITERATURE, BUPRENORPHINE/NALOXONE MAY BE CONSIDERED AS A FIRST-LINE AGENT IN PREGNANCY. BUPRENORPHINE/NALOXONE MICRO-DOSING MAY BE FAVOURED OVER A TRADITIONAL START TO AVOID WITHDRAWAL.

In 2020 a randomized controlled trial (RCT) was launched in Canada to contrast traditional versus micro-dose induction of OAT with buprenorphine/naloxone. The study goals are to measure withdrawal symptoms, adherence, durability of abstinence, and patient satisfaction, however pregnancy (as it is in most RCTs) is an explicit exclusion criterion.[65] [66] While maternity care organizations lobby for inclusion of pregnant persons in medical research, in the interim care necessarily requires action in the face of some uncertainty.

OAT providers can engage in a comprehensive risk-benefit discussion with patients, being clear about what is well known versus what is presumed to apply to OAT in pregnancy. Together an induction strategy that aligns with patient goals and prescriber experience can be developed.

- **Buprenorphine/naloxone may be superior to methadone**: Studies in this field are inherently fraught with low quality data, with case-control and retrospective studies comprising the majority of the literature. However, trends increasingly favour buprenorphine use particularly for its association with reduced care costs due to shorter hospital stays.[67]

TABLE 1: OBSTETRICAL OUTCOMES WITH BUPRENORPHINE VS METHADONE OAT - TWO CONSECUTIVE CASE SERIES[68]

METHADONE	OUTCOME	BUPRENORPHINE/NALOXONE
38w6d	Gestational Age @ birth	39w5d
2941 g	Newborn birth weight	3250 g
77.8%	Any NOWS	40.4%
52.8%	NOWS requiring medication	14.9%
19.7	Newborn days in hospital	9.4

- **Methadone is still an important treatment option**: High-dose unregulated opioid use may require methadone therapy[69] as these patients are not always sufficiently stabilized on buprenorphine/naloxone due to its "ceiling effect". Patients may have had negative experiences with buprenorphine in the past, or simply have a strong preference.[70] **Aligning with patient care goals has a more significant association with positive outcomes than use of one drug over the other**. While a comparison, as illustrated in TABLE 1, makes methadone appear dramatically inferior, the lack of high-quality evidence and importance of patient autonomy should preserve methadone as a reasonable care option according to a Cochrane review.[71]

- **Micro-dosing in pregnancy**: Micro-dosing induction of buprenorphine/naloxone is associated with increased access to OAT, reduced withdrawal symptoms, and rapid achievement of stabilization.[72] However, a literature review revealed only one paper,

reflecting a single case, regarding the safety of buprenorphine micro-dosing/rapid induction in pregnancy.[73]

Extrapolation from non-pregnant data is reasonable, however, **the risk of precipitated withdrawal is important to review during informed consent, given its association with prematurity**. Motivated and well-supported patients may be considered for outpatient induction.

TABLE 2: OUTPATIENT VS INPATIENT BUPRENORPHINE/NALOXONE INDUCTION IN PREGNANCY[74]

OUTPATIENT	OUTCOME	INPATIENT
0%	Precipitated withdrawal	13%
96%	Attend 1wk follow up	63%
72%	Buprenorphine positive urine at follow up	60%
53%	Illicit opioid positive urine at follow up	80%
87%	3-months adherence	63%

4) CYCLES OF USE AND WITHDRAWAL ARE ASSOCIATED WITH FETAL STRESS. THIS IS PRESUMED TO BE A CONSEQUENCE OF COMPROMISED PLACENTAL PERFUSION; PATIENTS SHOULD BE EDUCATED ABOUT THE IMPORTANCE OF AVOIDING WITHDRAWAL IN PREGNANCY AND REASSURED THAT THEIR PRESCRIBERS/OAT CARE TEAMS WILL TREAT THESE PRESENTATIONS.

Withdrawal relief is an important care goal on which providers and patients can often align, offering reassurance that opioid withdrawal is an appropriate indication for therapy. During pregnancy this discussion must be additionally nuanced as patients may be motivated to dose-restrict for fetal sparing. Self-induced suffering can be valued as "motherly sacrifice."

Opioid exposure in pregnancy modifies metabolic function of the placenta, likely through selective methylation, and can compromise oxygen delivery to the fetus overall.[75] The highs and lows of use and withdrawal impose acetylcholine vasoconstriction.[76] Given the maternal hypovolemia associated with acute withdrawal, placental perfusion is further compromised. Cerebral oxidative stress has been shown in animal models during fetal exposure to maternal opioid withdrawal.[77] [78]

OAT providers can reinforce the clinical importance of suppressed withdrawal from a recovery perspective, while also relieving mothers of the misconception that withdrawal is a necessary part of pregnancy. Withdrawal management in the obstetrical patient is most appropriate in a hospital setting with oral opioids as a bridge to OAT induction. Other medications to ameliorate symptoms can be utilized with the *exception of clonidine*. This potent antihypertensive is relatively contraindicated in pregnancy due to its association with hypotensive placental malperfusion.

5) COMMUNITY BASED OPIOID WEANING SHOULD BE LIMITED TO HIGHLY MOTIVATED PATIENTS WHO, AFTER THOROUGH RISK-BENEFIT DISCUSSION, DECLINE OAT THERAPY. CESSATION, EVEN IF CLOSELY SUPERVISED, IS EXTREMELY HIGH RISK FOR RELAPSE TO UNSTABLE OPIOID USE, MATERNAL OVERDOSE, AND PLACENTAL MALPERFUSION IMPOSED BY THE REQUISITE WITHDRAWAL.[79] [80] THIS APPROACH HAS ALSO NOT BEEN PROVEN TO IMPROVE NEWBORN OUTCOMES.[81]

Previous dogma linking "detoxification" (medication-assisted withdrawal for opioid-dependent patients[82]) with placental abruption have largely been disproven. The primary concern is with practical feasibility and **relapse risk**. Few patients actually complete the process and the overwhelming majority relapse to unstable use.[83]

However, in the interest of patient autonomy, for the highly motivated and very well-supported individual, cessation can be a treatment option with appropriate counselling. The term "detoxification" is predominantly used in the literature, but itself can have valuative connotations, as though OAT might be considered "intoxication." Identifying implicit bias is meaningful to empower patients to make care decisions based on their own values and not prejudices in the community.

Risks versus benefits of opioid cessation in pregnancy:

- Emerging studies suggest structural brain changes in opioid-exposed newborns, however findings are not yet clinically correlated to meaningful developmental effects; studies compare exposed and naive newborns, rather than OAT supported versus tapered pregnancies.[84]
- Acute maternal withdrawal results in high circulating catecholamines, uterine contractions and decreased placental perfusion which paradoxically increases fetal activity and oxygen demand. Similarly, lasting clinical consequences of these stress events are unknown.[85]
- In contrast with either OAT or unregulated use, cessation does not improve/affect rates of prematurity or NOWS severity.[86]
- Preoccupation with NOWS scoring can be a distractor – this condition is treatable and not associated with enduring sequelae. Neonatal sepsis, however, is increased 30-fold in unstable opioid use in pregnancy, and these risks should be considered when foregoing OAT.[87]
- Duration of symptomatic withdrawal can last up to 16 weeks which precipitates relapse[88]
- Maternal relapse rates are extremely high, up to **90% return to unstable use by delivery**.[89]

- **Risk of maternal death by overdose increases as OAT decreases; opioid tolerance is lost rapidly over days to weeks and what previously was a usual dose can become a lethal one**.[90]
- Only one study included fetal monitoring in its protocol, and did not reveal fetal distress, but this was too small to be representative.[91] Fetal effects of cessation are not well understood, and guidance is lacking. It is reasonable to refer to fetal assessment for a well-being scan if primary withdrawal results in prolonged dehydration, and to consider fetal heart auscultation during intervals of enduring maternal tachycardia or hypotension.
- Robust wrap-around supports with a culturally-safe care team are required for risk reduction.[92] This might include frequent check-ins either virtually or in-person regarding symptom tolerability, social stability, and mood assessment.
- Outpatient cessation is favoured given the lengthy time course. Recent study designs suggest 10% weekly or more, as per symptom profile.[96] **A safe and tolerable taper should not require inpatient intervention**.
- Preservation of the therapeutic alliance between patient and provider is essential and has a mortality benefit.[93] Patients who decline both OAT or a supported taper and either elect ongoing unregulated use or "cold-turkey" cessation need to know they still have a medical resource to return to when needs change or complications emerge.
- A contingency plan for OAT induction in the event of maternal/fetal distress should be in place. Where methadone and buprenorphine/naloxone are unavailable, slow-release oral morphine (SROM) and MS Contin can be acceptable off-label alternatives.[94]

One Canadian study followed a cohort of >100 pregnant patients who were offered long-acting morphine (SROM or MS Contin) on a taper with a goal of cessation.[95] **Fewer than 10% of participants were off of all opioids at the time of delivery**. Statistically significant outcomes included decreased birth weight, increased NOWS scores, and increased length of stay in the taper group.

Finally, rapid **inpatient** opioid tapers to zero over 7-14 days (so-called "detoxification admissions") are **NOT recommended for patients with OUD, and this includes pregnant patients with OUD**. Withdrawal management, or "detox", without transition to OAT and long-term treatment is associated with increased morbidity, such as HIV transmission, and mortality secondary to overdose.

If patients decline OAT despite the risks, a slow outpatient taper of opioids, as discussed above, is a safer approach than admission to a hospital or residential detox setting.

6) OPIOID USE IS OFTEN A BARRIER TO PRESENT FOR MATERNITY CARE.[96] PROVIDERS SHOULD ENCOURAGE THE USE OF ALL AVAILABLE COMMUNITY RESOURCES AND MAKE PROMPT REFERRALS TO MATERNITY CARE PROVIDERS WHO ARE FAMILIAR WITH OAT. THIS MAY INCLUDE AND IS OFTEN ENHANCED BY A SHARED-CARE APPROACH WITH OUTREACH NURSING, OBSTETRICIANS, MIDWIVES, AND ALLIED HEALTH.

Fear of stigma, infant apprehension, and lack of agency all collude to inhibit disclosure of opioid use in pregnancy. In addition to these more existential barriers to care, childcare is an important obstacle both for OAT adherences and prenatal (PN) care.[97] Medical adherence and maternity care attendance both improve when care occurs in the same place. Optimizing patient engagement can include shared OAT-PN care.

Patients describe moral inhibition around their use of OAT during pregnancy, the inclusion of this history on PN charts, and presumed stigma. "It is shamed-based, you know. You are made to feel ashamed for making poor choices and you have to carry that for the rest of existence."[98]

Stakes are also inflated during pregnancy with the threat of custody loss looming as an enduring stressor. "I had child protection tell me that if I relapsed one more time that they were going to take my children and I would never see them again… and that was it." For some patients this is a potent motivator, but for most it **recapitulates the powerlessness that is entrenched in marginalization, trauma, and addiction itself**. Evidence shows that child welfare agencies can unintentionally compromise recovery.[99]

Engagement with community support for cultural safety, group parenting programs to reduce isolation, and **reassurance that OAT is not reportable** can help bolster that vulnerability.

CLINICAL PEARL: VALUE OF TRUST

"Women in recovery from OUD may experience deeper engagement in outpatient perinatal services when they perceive that their providers are invested and collaboratively engaging in their recovery and personal growth." [100]

Cultivating trust in the setting of unregulated drug use is a clinical skill that OAT providers exercise with each care encounter – it is a particular type of expertise.

When patients transition to other providers – either for maternity care, antiviral treatment of their hepatitis, or an echo for their cardiomyopathy – OAT providers can help leverage that trust with shared-care encounters. Utilizing virtual platforms, the specialist can be invited into an OAT visit to create a setting of safety with a new face, protected from judgment and stigma by the provider they trust.

7) Smoking cessation counselling should be considered as a first-line intervention for pregnant smokers, given the synergistic harms of smoking and opioid use in pregnancy. To date there is sufficient safety evidence to also recommend bupropion and NRT in pregnancy.

OAT providers can debunk the myth that cessation should happen one substance at a time. Use is often paired, and concurrent use-reduction can improve outcomes synergistically. In pregnancy the most important co-use is cigarette smoking – a known teratogen with association with placental insufficiency. Smoking in pregnancy increases cardiac defects, limb malformations, and a variety of errors of visceral organogenesis.[101] Pulmonary compromise, reproductive impairment, and neurobehavioral effects last beyond childhood.[102]

As many as 95% of pregnant persons on OAT smoke cigarettes[103] with the lifetime cardiovascular maternal harms that smoking can impart.

Opioid use with concurrent smoking:

- Increases ectopic pregnancy rates.[104]
- Increases placenta previa and placental abruption.[91]
- Increases rates of miscarriage, stillbirth, and neonatal demise.[105]
- Increases premature birth, intrauterine growth restriction, and SIDS.[106] [107]

Smoking cessation in pregnancy:

- Is more likely to succeed with NRT which has good safety data.[108]
- May require higher NRT dosing due to increased nicotine metabolism.[109]
- Before 15-weeks gestation has the greatest magnitude of fetal benefit but cessation and use reduction at any gestational age also improve outcomes.[110]
- Patients may benefit from bupropion according to many observational trials and one small RCT.[111]
- Varenicline has insufficient data to recommend during pregnancy/breastfeeding.[112]

8) Symptoms common in pregnancy, such as nausea and vomiting, can be distressing and act as provocative triggers for relapse given their overlap with withdrawal symptoms. Antiemetics should be easily accessible and consider interval EKG studies to assess QT intervals for patients on OAT (particularly methadone) who require other QT-prolonging medication(s) for symptom control. Typically, non-sedating antiemetics are used first line. However, for severe symptoms a regimen utilizing more than one agent may be required.

Symptoms that resemble opioid withdrawal can induce panic in the recovering individual. Such symptoms, from morning sickness to hyperemesis, can decrease confidence that OAT is working, increase the need for QT-prolonging drugs, and can be exacerbated by the constipating effects of OAT.[113]

Increased Risk for Vomited Doses in Pregnancy

Given the ubiquity of nausea and vomiting in pregnancy (NVP), patients should be educated about the timing of emesis in relation to their OAT dose. Methadone and SROM are of particular concern, as a portion of the dose may be lost if the patient vomits within 15-20 minutes after dosing. Given that buprenorphine absorbs sublingually, vomiting is less of a concern for dosing stability if the dose was fully dissolved prior to emesis.

Regardless of the specific OAT medication, NVP is distressing to patients and warrants aggressive treatment. Vomited doses are also discussed in Ongoing Care, however **recommendations vary in pregnancy**, as described below:

- If NVP is a concern, consider pre-dosing with ondansetron 4-8 mg PO daily to prevent OAT dose losses, especially in the setting of hyperemesis gravidarum (HG).
- It may be useful for patients on methadone to consume 50% of their dose, wait 10 minutes in the pharmacy before consuming the rest, then wait another 10-15 minutes in pharmacy post dose. This way, if emesis occurs within 15 minutes after dosing, it can be observed by the pharmacist and be replaced appropriately in collaboration with the prescriber. Discussing this dosing arrangement with the pharmacist beforehand is essential, so as to make them aware of the situation and to consider the practical implications of having the patient wait in the pharmacy during the witnessed self-administration process.
- It is important to note that all replacement doses require a *new* OAT prescription. The prescriber should note that it is a "replacement dose" on the prescription.
- As some patients identify that certain smells/tastes trigger emesis, it may be helpful to speak with the pharmacist about trying a different diluent with the methadone concentrate (e.g., apple juice instead of Tang), or switching to a cherry-flavored concentrate that does not require dilution. However, remember that switching between methadone brands should be approached cautiously and in collaboration with the pharmacist. **Methadone products are not interchangeable from a clinical perspective nor a coverage perspective**. A new prescription would be required to switch a patient from one product to another. **Such changes will often require collaboration and communication between the prescriber, pharmacy team, and patient to monitor for dose equivalency.**
- Pregnant patients may also vomit take-home doses. **Pregnancy is the one circumstance in which a partial replacement dose may be considered for unwitnessed emesis.** Patients should be educated to check the time that they self-administer a take-home dose, so that they can report the time lapse between dosing and emesis more accurately. Ensure the patient has multiple contacts for assistance, particularly for dose losses due to unwitnessed emesis, to strategize the utility of a partial replacement dose.

- Treating NVP can be a key component of early treatment retention. Opioid withdrawal causes nausea that can exacerbate pregnancy-related nausea and vomiting. Vomiting is even more common during the induction phase of treatment. Therefore, during the induction and titration phase, dose retention is crucial to establish early benefit from treatment and to promote patient engagement.
- OAT providers should have a low threshold for referring pregnant patients starting OAT for IV rehydration in hospital or urgent care, as the combination of withdrawal and emesis may result in significant fluid deficits and affect overall coping.

Non-Prescription Treatment for NVP

Ginger in the form of tea, chews, and capsules are excellent first-line options for NVP. Acupressure and antihistamines are safe and effective. These methods should be exhausted before starting phenothiazines, dopamine, and serotonin 5-hydroxytryptamine type 3 receptor antagonists, particularly for QT-sparing in the setting of OAT.[114]

Many pregnant patients utilize cannabis for GI complaints. While the majority report symptom relief, **THC crosses the placenta readily and is associated with growth restriction, long-term neurobehavioral disorders, and an increased lifetime risk in the offspring for disordered substance use.** [115] [116] As such, national guidance discourages cannabis use in pregnancy.

Cannabinoid hyperemesis syndrome (CHS) has distinct clinical features from HG. CHS tends to be associated with significant pain, and features three phases of (1) abdominal pain prodrome, (2) emesis, and (3) exhaustion that tend to cycle through in 2-3 day intervals.[117] CHS rarely responds to traditional antiemetics, alleviated more by hot water bathing. The mainstay of therapy is cannabis cessation. HG on the other hand features nausea more prominently, is less cyclic in nature, responds to routine medications, and tends to improve after 20-weeks gestation. A simplified table below highlights features of CHS to distinguish it from HG. [118] [119] [120]

TABLE 3: DISTINGUISHING CANNABINOID HYPEREMESIS FROM HYPEREMESIS GRAVIDARUM IN PREGNANCY

HG	FEATURE	CHS
Primiparous non-smokers	Risk Factors	Cannabis >1x/wk for >1 year
First half of pregnancy	Gestational onset	Any gestational age
Absent	Pain Prodrome	Classic
Dextrose rehydration	Alleviating factors	Hot water bathing
H.Pylori co-infection	Aggravating factors	Increased cannabis use
Serotonin/dopamine antagonists	Effective medication	Limited role for medication

9) OUD PREDISPOSES PATIENTS TO HYPERALGESIA SO CONSULTATION WITH ANESTHESIA PRIOR TO DELIVERY SHOULD BE CONSIDERED.[121] OAT DOES NOT PROVIDE EFFECTIVE ANALGESIA IN LABOUR.

Patients have a variety of anxieties regarding analgesia in labour. They worry that they will be denied pain relief, that it will not be effective, and that opioid analgesia will cause them to relapse. Historically, OAT has been mistaken for pain control in labour, but current obstetrical guidance has clarified this matter. **Most importantly, opioids when used for acute pain in labour or post-operatively are not associated with OUD relapse**.[122]

Recommendations for analgesia in labour include:

- Analgesic activity of methadone and buprenorphine is much shorter (8 hours)[123] than that for withdrawal suppression. In pregnancy this can be even shorter due to metabolic acceleration. Again, it is important to recognize that the maintenance opioid for OUD is the baseline for preventing withdrawal and does not provide significant pain relief. As above, **patients on OAT with acute pain will typically require pain management in addition to their buprenorphine/naloxone or methadone dose**.
- Essentially all routine methods of analgesia are still available except for morphine in the patient on buprenorphine, as it may not have sufficient binding affinity to compete[124]. A remifentanil PCA can be offered for those who decline epidural.
- Despite opioid tolerance, patients can be reassured that acetaminophen and naproxen are usually sufficient postpartum for vaginal birth.[115]
- On average, patients on methadone require 70% more analgesia post c-section. Those on buprenorphine require a 47% increase.[125]
- Epidural is an excellent option for pregnant patients on OAT, and should be offered when appropriate.
- It is important to establish IV access early for patients with OUD in labour, as IV access may be challenging in individuals with a history of intravenous drug use.
- Pregnant patients on OAT should be referred for delivery in a center with the appropriate level of neonatal care capacity, as determined in consultation with the obstetrical care provider.

Delays in OAT dosing can cause unnecessary withdrawal on the labor delivery unit or birth center. In sufficiently stable patients, OAT providers may consider prescribing one take-home dose to be kept in the patient's hospital bag to bridge until reliable dosing is available.

Detailed recommendations for Managing Pain and the In-Hospital Care of individuals with OUD are discussed in these respective chapters.

10) Approach to infant nutrition should be weighed on an individual basis. OAT is not a contraindication to breastfeeding which is, in turn, associated with reduced NOWS scores and increased parent-infant bonding.[126] [127] [128] [129]

OAT providers are not expected to offer expertise in breastfeeding, but can support patient goals and reinforce that OAT is not a contraindication. In contrast, in the setting of unregulated opioid use, nursing is relatively contraindicated given the high risk for poisoned supply and unknown contaminants. It is unknown how long one should permit clearance before attempting to resume breastfeeding after an isolated use, particularly if methamphetamines contaminate the dose. This is an emerging field of active research and harm-reduction planning should be frank about what medicine does not yet know. However, **the benefit of skin-to-skin care in the first weeks of life is well demonstrated**; this helps to regulate newborn temperature and heart rate, allowing them to conserve calories for weight gain.

Maternal benefits of breastfeeding:[130]

- Decreased postpartum depression.*
- Increased maternal-newborn bonding.*
- Decreased postpartum bleeding.
- No cost, portable, complete nutrition for the first 6 months of life.
- Decreased risk of pregnancy in the first 6 months postpartum.
- Decreased lifetime risk of breast and ovarian cancers, diabetes, and hypertension.

Fetal benefits of breastfeeding:[131]

- Decreased NOWS severity.*
- Decreased SIDS.*
- Improved heart rate and temperature regulation.*
- Increased maternal-newborn bonding.*
- Reduced risk for respiratory infections.
- Decreased lifetime risk for type 1 diabetes, asthma, and obesity.

**These benefits can also be achieved at least in part with skin-to-skin bottle feeding.*

11) Opioid-involved pregnancies are high risk for postpartum depression and suicide. Screening for depression should occur at each trimester and postpartum follow up should be enhanced; patients should be screened by a care-provider within two weeks of delivery. Neither pregnancy nor breastfeeding are contraindications to SSRIs.

Maternal mortality is 8:100,000 and is 9% higher in Manitoba than the national average.[132] [133] This risk is increased to 20:100,000 for those who deliver a newborn symptomatic for NOWS.[134]

Most major centers offer robust services during antepartum, but routine postpartum follow up is limited to a solitary 6-week visit. In the opioid-involved pregnancy, it is the postpartum year that is the highest risk for psychosocial decompensation. Postpartum depression (PPD) impairs attachment and response to newborn cues[135] and has lasting consequences for attachment. **Due to anxiety about infant apprehension, mothers are reluctant to reach out for mental health supports**. The risk of depression, relapse, suicide, and unintentional overdose is effectively doubled amongst Indigenous populations.[18]

SSRIs are indicated for moderate to severe depression in pregnancy and postpartum, and are compatible with breastfeeding but associated with *slightly* increased NOWS scoring.[136] Given that suicide is a complication of undertreated depression, this small risk is appropriately accounted in risk-benefits assessment. **The exception is paroxetine which has been linked with equivocal findings of cardiac defects[137] and is generally avoided during pregnancy**. It is not contraindicated in breastfeeding. SSRIs with minimal QT-interval impact are favoured for patients on methadone. Education about and monitoring for serotonin syndrome is important for this population.[138]

TABLE 4: RISK FOR DEPRESSION, SUICIDE, AND OPIOID OVERDOSE IN THE OAT POPULATION.

RISK	GENERAL POPULATION	OAT POPULATION	RED FLAGS
PPD	5.6%[139]	32%[140]	Missed OAT doses
Suicidal Ideation	3-7%[141]	23%[142]	Repeat ED visits with non-specific complaints
Overdose	6.5:10,000[143]	281:10,000[130]	Loss to follow up

12) INTIMATE PARTNER VIOLENCE AND RELATIONSHIP DISCORD ARE HIGHLY CORRELATED WITH POSTPARTUM RELAPSE AND OVERDOSE. SCREENING FOR RELATIONSHIP STABILITY SHOULD OCCUR IN EACH TRIMESTER, WITH SAFETY PLANNING AS INDICATED.

Lamentably, pregnancy is the highest risk interval for intimate partner violence (IPV) over the reproductive lifespan, with increasing severity with advancing gestation. This is disproportionately burdensome for women with socioeconomic disadvantage. The general population has a risk of IPV in pregnancy of 9% whereas those living in poverty suffer 50%.[144]

Additionally, **for those dependent on opioids, lifetime risk of IPV is as high as 95% with violence in the past year up to 75%**.[145] This reveals a "bidirectional" risk where violence perpetuates increased unstable use, and instability is a key risk factor for violence. Adult male violence is a manifestation of childhood toxic stress and is modifiable[146] with often favourable outcomes with therapy and behaviour modification strategies; screening males for violent histories can potentially further reduce events suffered in peripartum.

CLINICAL PEARL: HARM REDUCTION ALONG THE CONTINUUM

Intimate partner violence increases postpartum suicidality by nine-fold.[147]

IPV care, such as safety shelters and support groups, often requires the patient to abstain from their relationship. As with opioid use, recovery from violence exists on a continuum with varied stages of readiness for change and actionable agency. Acceptance of referral may require time. In the interim, safety planning and advocating for patient agency fit well within the skills of the OAT provider - meeting patients where they are at, in a spirit of harm reduction.

Provider interventions to reduce maternal mortality due to IPV include:[148]

- **Universal screening (see Table 5) and referral for IPV**.
  - Collaborate on Safety Plans with patients.
  - Provide 24-hour crisis helpline in Manitoba (phone 1-877-977-0007).
  - Provide up-to-date shelter contact information, available at the Ending Violence Association of Canada link to Getting Help.

TABLE 5: HITS FOUR-QUESTION SCREENING TOOL FOR INTIMATE PARTNER VIOLENCE [149]

DOES YOUR PARTNER…	NEVER (1)	RARELY (2)	SOMETIMES (3)	OFTEN (4)	FREQUENTLY (5)
Hurt you					
Insult/talk down to you					
Threaten you with harm					
Scream/curse at you					

A total **score of 10** is considered "positive" for IPV

- **Recognize emergency room visits in the postpartum year as flags for IPV**. Optimize these encounters as opportunities for brief intervention and referral. Consider the role of traumatic brain injury in opioid recovery/relapse.[150]
- **Increase ease of access to naloxone kits** and treatment programming.
- **Refer to trauma informed community services**. Recognize the intergenerational and collective trauma lived by marginalized populations and offer culturally safe/embedded programming. See Managing Co-Occurring Psychiatric Disorders in OUD for a list of resources and additional guidance.

13) OAT IS NOT A REFLECTION OF PARENTING CAPACITY.[151,152,153] PATIENTS SHOULD BE OFFERED SUPPORT THROUGH LOCAL COMMUNITY PROGRAMS FOR PRENATAL AND/OR PARENTING CLASSES THAT ARE CULTURALLY SAFE AND ALIGNED WITH PARENTING VALUES. INVOLVEMENT OF CHILD PROTECTIVE SERVICES (CPS) SHOULD BE LIMITED TO DOCUMENTED UNSAFE BEHAVIOUR WITH INFANTS/CHILDREN ALREADY IN THE HOME. OAT IN PREGNANCY IS NOT AN INDICATION TO REPORT.

In 1997, a Manitoban case was escalated to the level of the Supreme Court[154] to assess whether or not illicit drug use in pregnancy was a reportable offense, and if child protection agencies could mandate treatment in service of the needs of an unborn child. In this instance, Manitoba's Queen's Bench had granted CPS the power to enforce involuntary residential addictions treatment, later revoked by the Supreme Court. This decision included harsh criticism of Manitoban courts, stating the "intervention was on behalf of the fetus with no evidence of concern for maternal wellbeing". Despite this highly publicized case and ruling, prevailing attitudes assume that women who use drugs in pregnancy lack maternal commitment, emotional maturity, and are inherently deceitful.[155]

Managing Misconceptions & Shame for Relapse Prevention

In the US, adoptive parent Barbara Harris founded Children Requiring a Caring Community, (CRACK, later termed Project Prevention), a program that pays women with addictions cash to engage in long-acting contraceptive use or undergo sterilization.[156] She was famously quoted on the television program *60 Minutes*, comparing her program to community neuter-spay clinics, and repeatedly used the phrase "having litters" in reference to the grand multiparity she observed in this population.[157] As of May 2021, over 7000 women with substance use histories had been paid to either accept an IUD or tubal ligation, and the initiative has branched into the United Kingdom. These attitudes are internalized by women of reproductive age, and can compound the self-loathing that often features in addiction:

> You can't be raised by an alcoholic, like there are people who have been raised by alcoholics and grown up to be good people, but those are stories you put in books and don't happen as often as you'd like to think. Then there are people who are raised by alcoholics, and become alcoholics because it's what they know, or that their kids go on welfare because their parents are on welfare – (16-year-old subject, Dee).[158]

Appreciating the myriad of reasons that women engage with unstable opioid use, and why pregnancy can stimulate recovery in some and relapse in others, is extremely poorly understood. We know there are important roles that familial substance use and childhood/intergenerational trauma play,[159] [160] but it is unclear how best to intervene and which risk factors can be modified in terms of impact.

A modicum of research has been committed to Indigenous communities, exploring the potential for intergenerational care in recovery. Formal "grannies", female elders who take on a

grandmotherly role, seem to increase care-engagement and fulfill a care gap left by the treatment community:

> I don't think, without Elders… our race our culture can survive. Let's face it, there are very few young people who are interested in culture nowadays. And with Elders like, no matter of how bad of a kid you are, almost all native kids looked up to their Kokum or their Mushum, almost all of them did – (17-year-old subject, Cherish).[149]

Indigenous doulas also appear in the literature as important advocates to navigate the inherent racial bias in medicine that influences maternity care and amplifies marginalization for OAT supported mothers. Their involvement can decrease barriers to care such as transportation needs, improve trust experiences in clinical environments, and help clients navigate encounters with CPS.[161]

This translates partly into relapse prevention planning between the patient and OAT provider. Extrapolating from alcohol-based literature, **shame is a potent risk factor for relapse** to unstable use.[162] Entering into pregnancy is not only triggering for old shame (such as childhood abuse[163]), but often exposes patients to countless microaggressions and direct insults about their capacity to parent. Erroneously, care providers may assume older children are in care, that fathers are not involved, and that the patient will not plan to parent.[152] Active listening, reframing, and fact-checking are important strategies to help patients navigate these hurts.

14) Infant apprehension is an important risk factor for maternal mortality in the opioid-involved pregnancy. If CPS are asked to assess for apprehension, wrap around supports are urgently indicated for maternal welfare.

Preservation of the mother-infant dyad and effective attachment requires "engaged mothering, recognition of risk, affection, and respectful maternity care". The result of attached parenting is increased discharge home of the newborn with biological family, experience of love and security, and increased enduring sobriety.[164] OAT providers can validate patient parenting goals and priorities, reinforce the role of motherhood, and help patients navigate local supports to prepare for parenting. However, at the time of delivery, unanticipated intervention from CPS can be intensely destabilizing to the family unit and to maternal recovery and psychiatric safety.

Increased PPD & Unintentional Overdose

Postpartum patients with a substance use history are subjected to disproportionate monitoring and apprehension from child protection agencies.[165] [166] **Infant removal is not simply "distressing" but is experienced with equally intense grief symptoms as those endured when an infant has died**.[167] The impact of this complex grief experience is measured in PPD (effectively doubled[168]) and unintentional overdose that is increased by 55% and further doubled in the Indigenous population[169] in the setting of apprehension.

Nearly 90% of children in foster care in Manitoba are Indigenous,[170] linking to intergenerational traumas like the Residential School Act and Sixties Scoop.[171]

The most significant risk factors for permanent loss of parental custody are more important in combination rather than any single factor, and include:[172]

a) Incarceration history with comorbid substance use.

b) Maternal childhood abuse history with less than grade 12 education.

c) Psychiatric history requiring hospitalization in setting of depressive symptoms.

These patients require multidisciplinary care throughout pregnancy and long into the postpartum period. Collaboration with social work, spiritual care, grief counseling and culturally appropriate community programs such as The Mothering Project are essential.

One of the most important protective factors for preserved custody is simply rooming-in with easy and close contact and skin-to-skin engagement with the newborn. "Given that a growing body of literature suggests rooming in can reduce NAS scores, and that higher NAS scores are associated with an increased risk of maternal overdose, we believe rooming in should be considered a critical factor in future analyses looking at risk for maternal overdose."[173] Champions for the maternal-infant dyad are required at the level of patient care and hospital policy.

15) Tapering OAT within the first postpartum year is highly correlated with relapse and unintended overdose. Patients should be advised to titrate dose to effect as they would non-pregnant, and encouraged to postpone plans to taper their OAT dose until the newborn is over one year of age.

Postpartum relapse risk in the setting of an OAT-supported pregnancy is high, along with the risk for fatal overdose.[174]

Traumatic birth experiences increase this risk,[175] and sleep deprivation with the intense demands of new parenting certainly play a role,[176] but there are also counterintuitive risks with addiction treatment. Residential treatment during pregnancy is *negatively correlated* with treatment retention and custody beyond the first 6 months of life.[177] Those supported in the community on OAT had significantly improved outcomes, without the dose itself impacting the result.

Risk features in the postpartum year:

- 1:7 will experience overdose.[11]
- The risk of overdose increased by 4x after the first 6 months of life.[10]
- Indigenous ethnicity increases postpartum overdose by 2.1x.[178]

Red flags for relapse: [179]

- Bottling up emotions,
- Socially isolating,
- Failing to attend/participate in programming,
- Focusing on others rather than self, and
- Poor eating/sleeping habits.

Relapse prevention: [180]

- Changing lifestyle/environment to make it easier to avoid use,
- Being completely honest,
- Asking for help,
- Practicing self-care, and
- Avoiding rule bending.

There is very little in the literature to guide clinicians about when it is advisable to consider weaning OAT in general, and even less regarding the postpartum family. Recommendations, such as the recent publication from Mayo Clinic,[181] lump together multiple populations on opioids such as those treated for chronic pain and OUD across the age continuum.

Again, OUD is a chronic medical condition that requires long-term treatment, and no recommendations exist to indicate a specific optimal treatment duration. However, it is encouraged and recommended that treatment continue for as long as desired by the patient to provide stability, functionality, and reduce harms. See Discontinuing Treatment for guidance on helping patients decide when to attempt tapering and detailed recommendations for withdrawal of OAT.

Patient goals, functional/quality of life impairments, polypharmacy, or cardiovascular complications of opioid use may all be motivators to taper, but must outweigh the risk of destabilizing recovery. Ensuring stability in other domains, such as housing, income, relationships, mental health, and custody, are all likely protective features to increase the likelihood of a successful taper, but data in this area is scarce and poorly nuanced. Case-by-case risk-benefits analysis is required, as is reassurance that OAT support can be an important feature of a healthy and happy home.

CLINICAL PEARL: COMPASSION IS AS IMPORTANT AS OAT IN THE OPIOID-INVOLVED PREGNANCY

I think you should know that your belief in me and your kindness and your non-judgement played a huge part in how my life is today. When I first met you, I thought of myself as worthless and was quite used to being treated that way by every person that I had come in contact with. Your easy kindness was felt immediately, and I remember that you gave me that shred of hope that I so desperately needed. Somehow 'thank you' seems hardly sufficient. (Former patient BC Women's Fir Square, 2005)[17].

FURTHER CONSIDERATIONS & ONGOING AREAS OF RESEARCH

SROM In Pregnancy

SROM (name brand Kadian®) is an oral alternative to methadone and buprenorphine/naloxone and regarded as a *third-line therapy* in the general population. There is scant literature regarding the utility of SROM in non-pregnant individuals and even less regarding OAT with SROM in pregnancy.

- **Consideration of RISK**: A Cochrane Review conducted in 2013 identified only three studies, representing 197 *non-pregnant* subjects comparing first-line OAT with SROM. These demonstrated relatively equivalent outcomes regarding remission and treatment engagement, but identified significantly worse abdominal cramping, aches & pains, insomnia and (in one study) depression with SROM compared to methadone and buprenorphine.[182] Given the predisposition to these complaints inherent to pregnancy, there is concern that the side effects of SROM could be deleterious. In two small observational studies in the late 1990s, however, this was not the case.[183]
- **Anticipation of BENEFIT**: One observational trial followed 24 pregnancies supported on SROM and *no clinically significant* maternal or newborn differences were found in contrast to buprenorphine and methadone.[184] However, there are also practical and safety issues to consider for SROM in comparison with first-line therapy.

Practical Considerations of SROM

Like other forms of OAT, **daily witnessed dosing is required with SROM**. With TID induction, short-term hospital admission may be considered for safety. However, for community-based induction once-daily dosing and subsequent titration of SROM is preferred. Frequent clinical assessment is required for safety. If the pregnant patient is *agreeable to admission,* the following titration approach is recommended as applicable:

- **If the daily use is relatively consistent and dosing is known**:
    - Convert to equivalent dose of short-acting liquid morphine (for ease of witnessed administration in hospital and to reduced risk of diversion).
    - Reduce equivalent dose of liquid morphine by 50% (due to incomplete cross tolerance when switching to a new opioid).
    - Divide into three scheduled doses of immediate-release (IR) liquid morphine.
    - Add three PRN doses of liquid morphine (30-50% of scheduled dose).
- **Alternatively, if no consistent daily dose is known** (i.e., variable daily dose depending on availability or uncertainty regarding use history):

    - Start with a smaller dose (e.g., 15 mg IR liquid morphine TID with 5 mg liquid morphine TID PRN).
- **Titrate similarly to the** Conventional Buprenorphine Induction:
    - Tabulate all of Day 1 scheduled + PRN doses to a 24-hour total consumed.
    - Divide total value into three scheduled doses.
    - Add three PRN doses of 5-15 mg TID (again, utilize liquid morphine as above).
- **Once an optimal dose is reached** (opioid withdrawal is adequately suppressed for 24 hours), convert daily IR liquid morphine dose to equivalent daily SROM.

See Alternative Treatment Approaches to OUD for further SROM guidance.

STRONG RECOMMENDATION: BUPRENORPHINE VS SROM IN RURAL & REMOTE COMMUNITIES

When no local access to traditional OAT programs exists in rural/remote locations for pregnant patients agreeable to buprenorphine/naloxone, local care providers are strongly encouraged to reach out to regional and urban OAT services to explore options for shared care. Buprenorphine/naloxone could be prescribed virtually, in partnership with the local care providers who can provide the in-person assessment/support.

RAAM clinics or RAAM on-call services, the HSC Addiction Medicine Consult Service on-call physician, and the MOST program are all valuable resources. These resources can be explored to arrange OAT access for pregnant patients living in rural or remote areas. When limited pharmacy/nursing station access makes daily witnessed dosing impractical, liberal prescribing of buprenorphine/naloxone with multiple early take-home doses is preferred over take-home doses of SROM, as the latter poses a much greater safety risk to the patient and local community, in comparison.

However, given barriers to access especially for rural/remote communities, SROM is a reasonable model for OAT in pregnancy where conventional treatment with buprenorphine or methadone is refused, or has failed, or is not practically accessible, either as a bridging strategy or for ongoing maintenance. It is important to note that access to daily witnessed dosing of SROM is required for patient and community safety. Given safety concerns regarding opioid tapering in pregnancy and postpartum, utilizing SROM to this end must only be considered in careful consultation, on a case-by-case basis, with an addiction medicine specialist.

Sublocade® In Pregnancy

Sublocade® (buprenorphine extended-release) is a depot injection, administered subcutaneously once per month to replace buprenorphine/naloxone dosing up to 24 mg daily. Presently, there is no dose equivalency for patients requiring 26-32 mg daily.

- **Consideration of RISK**: In general, pregnancy and breastfeeding have been viewed as relative contraindications to Sublocade®, as one of its excipients, *N*-methyl-pyrrolidone (NMP), has been identified as potentially teratogenic in animal studies. Human data is extremely limited: two cases of undiagnosed pregnancy treated with Sublocade®, up to 18 weeks gestation, had normal obstetrical and pediatric outcomes.[185]
- **Anticipation of BENEFIT**: The motivation to explore Sublocade® in pregnancy is not only for the perceived benefits that apply to non-pregnant patients (more stable steady-state than daily dosing, fewer pharmacy visits and associated stigma, and reduced risk for theft/diversion of sublingual tablets).[186] The pharmacokinetics are also theorized to result in decreased neonatal withdrawal severity. Clinical trials of a novel formulation without NMP are underway at the time of writing. CAM2038 has a weekly depot formulation that replaces NMP with ethanol at a clinically irrelevant concentration; the maximum fetal exposure over 9 months gestation is one tablespoon.[187] This is being studied in a randomized control trial compared with daily sublingual buprenorphine/naloxone.

Practical Considerations for Sublocade®

It is not uncommon to have breakthrough withdrawal during the first month of Sublocade® treatment, requiring supplementation with sublingual buprenorphine/naloxone.[188] For some patients, breakthrough withdrawal may even last longer than the first month of treatment. This may obviate some of the improved convenience of Sublocade® during pregnancy. In a case series with three subjects, Sublocade® started after 12 weeks gestation produced euphoria in the first 1-3 days post injection similar to intoxication.[189] This was **not** observed in the case study of Sublocade® use prior to pregnancy diagnosis, but does amplify the controversy surrounding this method of treatment. Reliable data is not expected to be imminently available.

STRONG RECOMMENDATION: USE OF SUBLOCADE® IN PREGNANCY

Given the paucity of data for antepartum efficacy, maternal tolerance, and fetal safety, introduction to Sublocade® during pregnancy should be deferred to the postpartum interval.

Continuation of Sublocade® may be considered when pregnancy is identified after treatment is well-established with Sublocade®, if alternative therapy is not available, and gestation is already greater than 12 weeks (beyond embryogenesis). Patients who are breastfeeding are encouraged to further defer until 6 months postpartum when breastfeeding is no longer exclusive nutrition.

As data emerges, these STRONG RECOMMENDATION statements will be revised accordingly.

IN SUMMARY

Pregnancy can be a very motivating but equally challenging time for patients with OUD.

OAT providers are encouraged to support individuals throughout pregnancy and postpartum with compassion, non-judgment, and collaboration, while utilizing the evidence-based best practices discussed in this chapter. Using a patient-centered, trauma-informed, harm-reduction, and culturally-safe approach is essential, as with all patients on OAT. The OAT provider and team can be effective advocates for pregnant patients, promoting autonomy, agency, and comprehensive care during a vulnerable time in their patients' lives.

References

[1] Unger, A., Jung, E., Winklbaur, B., & Fischer, G. (2014). Gender issues in the pharmacotherapy of opioid-addicted women: buprenorphine. In *Women, Children, and Addiction* (pp. 113-126). Routledge.

[2] Campbell, J., Matoff-Stepp, S., Velez, M. L., Cox, H. H., & Laughon, K. (2021). Pregnancy-associated deaths from homicide, suicide, and drug overdose: review of research and the intersection with intimate partner violence. *Journal of Women's Health*, *30*(2), 236-244.

[3] https://www.health.gov.bc.ca/library/publications/year/2015_a/pt-centred-care-framework.pdf

[4] Staff, A., Volunteers, K. O. P., & KOB, B. (2016). Klinic Community Health's Statement on Trauma-Informed Practice. https://trauma-informed.ca/wp-content/uploads/2013/10/Trauma-informed_Toolkit.pdf

[5] Maté, G. (2008). *In the realm of hungry ghosts: Close encounters with addiction*. Random House Digital, Inc.

[6] Mateu-Gelabert, P., Guarino, H., Jessell, L., & Teper, A. (2015). Injection and sexual HIV/HCV risk behaviors associated with nonmedical use of prescription opioids among young adults in New York City. *Journal of substance abuse treatment*, *48*(1), 13-20.

[7] https://www.catie.ca/sites/default/files/2022-01/CATIE_SaferSexGuide_2022_English_WEB.pdf Accessed Feb 20. 2022

[8] Bourgeois, A. C., Edmunds, M., Awan, A., Jonah, L., Varsaneux, O., & Siu, W. (2017). Can we eliminate HIV?: HIV in Canada—surveillance report, 2016. *Canada Communicable Disease Report*, *43*(12), 248.

[9] Barral, M. F et al (2014). Risk factors of HIV-1 vertical transmission (VT) and the influence of antiretroviral therapy (ART) in pregnancy outcome. *Revista do Instituto de Medicina Tropical de Sao Paulo*, *56*(2), 133–138.

[10] Mohd Salleh NA, Fairbairn N, Nolan S, et al. Dispensation of antiretroviral therapy and methadone maintenance therapy at the same facility in a low-barrier setting linked to optimal adherence to HIV treatment. *HIV Medicine*. 2019; in press.

[11] Remis RS. *Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007*. Ottawa, ON: Public Health Agency of Canada; 2007. Available from: www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/ model07-eng.pdf. Accessed 2015 Apr 10.

[12] Gordon, J., Bocking, N., Pouteau, K., Farrell, T., Ryan, G., & Kelly, L. (2017). First Nations hepatitis C virus infections: Six-year retrospective study of on-reserve rates of newly reported infections in northwestern Ontario. *Canadian Family Physician*, *63*(11), e488-e494.

[13] Boucher, M & Gruslin, A No. 96-The Reproductive Care of Women Living With Hepatitis C Infection *SOGC Clinical Practice Guidelines*. 2017; 39(7): E1-E25.

[14] Wong S, Ordean A, Kahan M, SOGC clinical practice guidelines: Substance use in pregnancy: no. 256, April 2011.*Int J Gynaecol Obstet*. 2011 Aug; 114(2):190-202.

[15] Binka, M., Butt, Z. A., Wong, S., Chong, M., Buxton, J. A., Chapinal, N., & Janjua, N. Z. (2018). Differing profiles of people diagnosed with acute and chronic hepatitis B virus infection in British Columbia, Canada. *World Journal of Gastroenterology*, *24*(11), 1216.

[16] Centers for Disease Control and Prevention. Washington, DC: Public Health Foundation; 2015. *Chapter 10: Hepatitis B*. Jennifer Hamborsky, Kroger A, Wolfe C, editors. Epidemiology and prevention of vaccine preventable diseases. 13th ed.

[17] Tram T. Tran, Hepatitis B in Pregnancy, *Clinical Infectious Diseases*, Volume 62, Issue suppl 4, June 2016, Pages S314–S317

[18] Antiretroviral Pregnancy Registry Steering Committee. *Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 July 2015*. Wilmington, NC: Registry Coordinating Center, 2015. Accessed 6 February 2016

[19] Han G-R , Cao M-K, Zhao W et al. A prospective and open label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. *J Hepatology.* 2011; 55:1215–21.

[20] Giovannetti J. Alberta declares provincewide syphilis outbreak amid surge across Canada. *Globe and Mail* (Calgary Ed.) [Internet]. 2019 Jul 17 [cited 2022, Feb 20].

[21] Traeger MW, Cornelisse VJ, Asselin J, et al. Association of HIV preexposure prophylaxis with incidence of sexually transmitted infections among individuals at high risk of HIV infection. *JAMA*. 2019;321(14):1380–90.

[22] Mill, J, Singh AE, Taylor M. Women in the shadows: prenatal care for street-involved women. *Can J Urban Res*. 2012;21(2):68–89.

[23] Torrone, E.A. and W.C. Miller, Congenital and Heterosexual Syphilis: Still Part of the Problem. *Sexually Transmitted Diseases*. 2018. 45: p. S20-S22

[24] Park, E., Yip, J., Harville, E., Nelson, M., Giarratano, G., Buekens, P., & Wagman, J. (2021). *Gaps in the Congenital Syphilis Prevention Cascade*. Qualitative Findings from Kern County, California.

[25] Brown, Laura S. Not Outside the Range: One Feminist Perspective on Psychic Trauma. *Trauma: Explorations in Memory*. Ed. Cathy Caruth. Baltimore: Johns Hopkins UP, 1995.100-12

[26] Jones HE, Deppen K et al. Clinical care for opioid-using pregnant and postpartum women: the role of obstetric providers. *Am J Obstet Gynecol*. 2014 Apr; 210(4):302-310.

[27] Grande LA, Thompson EC, Au MA, Sawyer D, Baldwin L-M, Rosenblatt R. Problem Drug-related Behavior and Discontinuation of Opioids Following the Introduction of an Opioid Management Program. *J Am Board Fam Med.* 2016;29(6):718–726. pmid:28076255

[28] Benningfield MM et al Co-occurring psychiatric symptoms are associated with increased psychological, social, and medical impairment in opioid dependent pregnant women. *Am J Addict*. 2010 Sep-Oct; 19(5):416-21

[29] Spyridou, A., Schauer, M., & Ruf-Leuschner, M. (2015). Obstetric care providers are able to assess psychosocial risks, identify and refer high-risk pregnant women: validation of a short assessment tool–the KINDEX Greek version. *BMC pregnancy and childbirth*, *15*(1), 1-17.

[30] Chatterjee, A., Yu, E. J., & Tishberg, L. (2018). Exploring opioid use disorder, its impact, and treatment among individuals experiencing homelessness as part of a family. *Drug and Alcohol Dependence*, *188*, 161-168.

[31] E Charron, et al. It's a very nuanced discussion with every woman: Health care providers' communication practices during contraceptive counseling for patients with substance use disorders. *Contraception*, 102 (2020), pp. 349-355

[32] Canadian Institute for Health Information. *Opioid-Related Harms in Canada* [Internet]. CIHI, Ottawa, ON, 2017. https://secure.cihi.ca/free_products/opioid-harms-chart-book-en.pdf

[33] Statistics Canada. *Table 102-0551 Deaths and mortality rate, by selected grouped causes* [Internet]. 2018. https://www150.statcan.gc. ca/t1/tbl1/en/tv.action?pid=1310039201. Accessed February 20, 2022

[34] Committee opinion No. 711: Opioid use and opioid use disorder in pregnancy. *Obstet Gynecol*. 2017;130(2):e81-e94

[35] Guttmann, A., Blackburn, R., et al. (2019). Long-term mortality in mothers of infants with neonatal abstinence syndrome: A population-based parallel-cohort study in England and Ontario, Canada. *PLoS medicine*, *16*(11), e1002974.

[36] Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. In: *Medication-assisted treatment for opioid addiction in opioid treatment programs*. Treatment Improvement Protocol (TIP) Series, No. 43 . Rockville (MD): Substance Abuse and Mental Health Services Administration; 2005. p. 211–24.

[37] Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. *Obstet Gynecol*. 2013;122(4):838-844

[38] Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol*. 2011;204(4):314.e1-314.e11.

[39] Shaw GM, Malcoe LH, Swan SH, Cummins SK, Schulman J. Congenital cardiac anomalies relative to selected maternal exposures and conditions during early pregnancy. *Eur J Epidemiol* 1992;8:757–60

[40] Nezvalova-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. *Eur J Clin Pharmacol* 2011;67:1253–61

[41] Caritis, S. N., & Panigrahy, A. (2019). Opioids affect the fetal brain: reframing the detoxification debate. *American journal of obstetrics and gynecology*, *221*(6), 602-608.

[42] Newman RG Methadone treatment. Defining and evaluating success. N Engl J Med. 1987 Aug 13; 317(7):447-50

[43] Marshall BD, et al (2011). Reduction in overdose mortality after the opening of North America's first medically supervised safer injecting facility: a retrospective population-based study. *Lancet*. 377(9775):1429-1437

[44] Kaltenbach K, Berghella FL. Opioid dependence during pregnancy: effects and management. *Ob Clinics of NA.* 1998 March;25(1)

[45] ACOG Committee on Health Care for Underserved Women. (2012). ACOG Committee Opinion No. 524: opioid abuse, dependence, and addiction in pregnancy. *Obstetrics and gynecology*, *119*(5), 1070-1076.

[46] Lindsay MK, Burnett E The use of narcotics and street drugs during pregnancy. *Clin Obstet Gynecol*. 2013 Mar; 56(1):133-41.

[47] Nathoo, T., et al (2015) *Harm Reduction and Pregnancy: Community-based Approaches to Prenatal Substance Use in Western Canada*: University of Victoria School of Nursing and British Columbia Centre of Excellence for Women's Health.

[48] Velez, M., & Jansson, L. M. (2008). The opioid dependent mother and newborn dyad: non-pharmacologic care. *Journal of addiction medicine*, *2*(3), 113.

[49] Bagley SM, Wachman EM, Holland E, Brogly SB. Review of the assessment and management of neonatal abstinence syndrome. *Addict Sci Clin Pract.* 2014;9:19

[50] Kandall SR, Akbin RS, Gartner LM, Lee KS, Eidelman A, Lowinson J, et al. The narcotic dependent mother: fetal and neonatal consequences. *Early Hum Develop.* 1977;1:159–169

[51] Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. In: *Medication-assisted treatment for opioid addiction in opioid treatment programs*. Treatment Improvement Protocol (TIP) Series, No. & Rockville (MD): Substance Abuse and Mental Health Services Administration; 2005. p. 211–24

[52] McCarthy JJ, Leamon MH, Finnegan LP, Fassbender C (2017) Opioid dependence and pregnancy: minimizing stress on the fetal brain. *Am J Obstet Gynecol*. Mar; 216(3):226-231.

[53] Balfour-Boehm J, Rea S, Gordon J, Dooley J, Kelly L, Robinson A. The evolving nature of narcotic use in northwestern Ontario. *Can J Rural Med* 2014;19(4):158-60.

[54] Jumah NA, Edwards C, Balfour-Boehm J, Loewen K, Dooley J, Gerber-Finn L, et al. Observational study of the safety of buprenorphine and naloxone in pregnancy in a rural and remote population. *BMJ Open* 2016;6(10):e011774

[55] Ordean, A., Wong, S., & Graves, L. (2017). No. 349-substance use in pregnancy. *Journal of Obstetrics and Gynaecology Canada*, *39*(10), 922-937.

[56] American College of Obstetricians and Gynecologists. (2017). *ACOG Committee Opinion, Number 711. Opioid use and opioid use disorder in pregnancy*. ACOG.org.

[57] National Institute for Health and Clinical Excellence. *Drug misuse: psychosocial interventions* London: NICE, 2007.

[58] O'Connor, M., Czarnik, M., Morrow, B., & D'Angelo, D. (2021). Opioid use during pregnancy: An analysis of comment data from the 2016 Pregnancy Risk Assessment Monitoring System survey. *Substance abuse*, 1-8.

[59] Radel, L., Baldwin, M., Crouse, G., Ghertner, R., & Waters, A. (2018). Substance use, the opioid epidemic, and the child welfare system: Key findings from a mixed methods study. *Washington, DC: Office of the Assistant Secretary for Planning and Evaluation*.

[60] Jones HE, O'Grady KE, Malfi D, Tuten M. Methadone maintenance vs. methadone taper during pregnancy: maternal and neonatal outcomes. *Am J Addict*. 2008 Sep-Oct;17(5):372-86

[61] Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. In: *Medication-assisted treatment for opioid addiction in opioid treatment programs*. Treatment Improvement Protocol (TIP) Series, No. 43 . Rockville (MD): Substance Abuse and Mental Health Services Administration; 2005. p. 211–24

[62] Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL. Altered methadone pharmacokinetics in methadone-maintained pregnant women. J *Pharmacol Exp Ther*. 1985;233:1–6

[63]Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL J (1985) Altered methadone pharmacokinetics in methadone-maintained pregnant women. *Pharmacol Exp Ther*. 1985 Apr; 233(1):1-6.

[64] Caritis, et al (2017). An evidence-based recommendation to increase the dosing frequency of buprenorphine during pregnancy. *American journal of obstetrics and gynecology*, *217*(4), 459-e1.

[65] Wong, J. S., Nikoo, M., Westenberg, J. N., Suen, J. G., Wong, J. Y., Krausz, R. M., … & Azar, P. (2021). Comparing rapid micro-induction and standard induction of buprenorphine/naloxone for treatment of opioid use disorder: protocol for an open-label, parallel-group, superiority, randomized controlled trial. *Addiction Science & Clinical Practice*, *16*(1), 1-10.

[66] Moe, J et al. (2020). Microdosing and standard-dosing take-home buprenorphine from the emergency department: a feasibility study. *Journal of the American College of Emergency Physicians Open*, *1*(6), 1712-1722.

[67] Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, O'Grady KE, Selby P, Martin PR, Fischer G Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med.* 2010 Dec 9; 363(24):2320-31.

[68] J. Kakko et al. Buprenorphine and methadone treatment of opiate dependence during pregnancy: Comparison of fetal growth and neonatal outcomes in two consecutive case series. *Drug and Alcohol Dependence.* 96 (2008) 69–78

[69] Thomas CP, Fullerton CA, Kim M, Montejano L, Lyman DR, Dougherty RH, Daniels AS, Ghose SS, Delphin-Rittmon ME Medication-assisted treatment with buprenorphine: assessing the evidence. *Psychiatr Serv.* 2014 Feb 1; 65(2):158-70.

[70] Holbrook, A. M. (2015). Methadone versus buprenorphine for the treatment of opioid abuse in pregnancy: science and stigma. *The American journal of drug and alcohol abuse*, *41*(5), 371-373.

[71] Minozzi S, Amato L, Bellisario C, et al. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev.* 2013; 94: CD006318

[72] Ahmed, S., Bhivandkar, S., Lonergan, B. B., & Suzuki, J. (2021). Microinduction of buprenorphine/naloxone: a review of the literature. *The American Journal on Addictions*, *30*(4), 305-315.

[73] Irwin, M., Petersen, K. S., & Smith, M. A. (2021). Rapid buprenorphine induction for cancer pain in pregnancy. *Journal of Palliative Medicine*, *24*(8), 1257-1262.

[74] Kelly, J. , Raghuraman, N. ,et al (2021). Home Induction of Buprenorphine for Treatment of Opioid Use Disorder in Pregnancy. *Obstetrics & Gynecology, 138* (4)

[75] Rosenfeld, C. S. (2022). *The placenta as a target of opioid drugs*. Biology of reproduction.

[76] Sastry, B. V. (1991). Placental toxicology: tobacco smoke, abused drugs, multiple chemical interactions, and placental function. *Reproduction, Fertility and Development*, *3*(4), 355-372.

[77] Pan, J. et al. Oxidative stress in heroin administered mice and natural antioxidants protection. *Life Sci.* 77, 183–193 (2005)

[78] Hamdy, M. M., Elbadr, M. M. & Barakat, A. Bupropion attenuates morphine tolerance and dependence: Possible role of glutamate, norepinephrine, inflammation, and oxidative stress. *Pharmacol Rep*. 70, 955–62. (2018)

[79] McCarthy JJ, Leamon MH, Finnegan LP, Fassbender C: Opioid dependence and pregnancy: Minimizing stress on the fetal brain. *Am J Obstet Gynecol* 2017;216:226–231.

[80] McCarthy JJ: Intrauterine abstinence syndrome (IAS) during buprenorphine inductions and methadone tapers: Can we assure the safety of the fetus? *J Matern Neonatal Med.* 2012;25:109–112

[81] Terplan, M., Laird, H. J., Hand, D. J., Wright, T. E., Premkumar, A., Martin, C. E., ... & Krans, E. E. (2018). Opioid detoxification during pregnancy: a systematic review. *Obstetrics and gynecology,* 131(5), 803.

[82] Wong S, Kahan M, Ordean A. *Substance use in pregnancy*. Ottawa, ON: SOGC 2011

[83] Opioid use and opioid use disorder in pregnancy. Committee Opinion No. 711. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2017;130:e81–94

[84] Caritis, S. N., & Panigrahy, A. (2019). Opioids affect the fetal brain: reframing the detoxification debate. *American journal of obstetrics and gynecology*, *221*(6), 602-608.

[85] Bailey, B. A., Shah, D. S., Boynewicz, K. L., Justice, N. A., & Wood, D. L. (2022). Impact of in utero opioid exposure on newborn outcomes: beyond neonatal opioid withdrawal syndrome. *The Journal of Maternal-Fetal & Neonatal Medicine*, 1-8.

[86] Wang, M et al. Opioid Detoxification during Pregnancy: Systematic Review and Meta-Analysis of Maternal and Neonatal Outcomes [11R]. *Obstetrics & Gynecology.* 131 (2018): 197S.

[87] Bailey, B. A., Shah, D. S., Boynewicz, K. L., Justice, N. A., & Wood, D. L. (2022). Impact of in utero opioid exposure on newborn outcomes: beyond neonatal opioid withdrawal syndrome. *The Journal of Maternal-Fetal & Neonatal Medicine*, 1-8.

[88] Terplan, M., Laird, H. J., Hand, D. J., Wright, T. E., Premkumar, A., Martin, C. E., ... & Krans, E. E. (2018). Opioid detoxification during pregnancy: a systematic review. *Obstetrics and gynecology,* 131(5), 803.

[89] Saia KA, Schiff D, Wachman EM, Mehta P, Vilkins A, Sia M, et al. Caring for pregnant women with opioid use disorder in the USA: expanding and improving treatment. *Curr Obstet Gynecol Rep.* 2016;5:257–63 .

[90] (1) Committee on Obstetric Practice. Committee Opinion No. 711: Opioid Use and Opioid Use Disorder in Pregnancy*. Obstet Gynecol* 2017 Aug;130(2):e81-e94; (2) Rodriguez CE, Klie KA. Pharmacological treatment of opioid use disorder in pregnancy. *Semin Perinatol.* 2019; (3) Klaman S, Isaacs K, Leopold A, Perpich J, Hayashi S, Vender J, et al. Treating Women Who Are Pregnant and Parenting for Opioid Use Disorder and the Concurrent Care of Their Infants and Children: Literature Review to Support National Guidance. *J Addict Med* 2017;11(3):178-190

[91] LePreau, F. J., GARVEY, B., PAULL, N., & STEIN, M. D. (1995). Opiate detoxification of pregnant women using clonidine: an observational cohort study. *Journal of Women's Health*, 4(4), 381-386.

[92] Terplan, M., et al. (2018). Opioid detoxification during pregnancy: a systematic review. *Obstetrics and gynecology*, *131*(5), 803.

[93] Jones HE, Deppen K et al Clinical care for opioid-using pregnant and postpartum women: the role of obstetric providers. *Am J Obstet Gynecol.* 2014 Apr; 210(4):302-310

[94] Fischer G, Jagsch R, Eder H, et al. Comparison of methadone and slow-release morphine maintenance in pregnant addicts. *Addiction*. 1999;94:231-9

[95] Dooley, R., Dooley, J., Antone, I., Guilfoyle, J., Gerber-Finn, L., Kakekagumick, K., ... & Kelly, L. (2015). Narcotic tapering in pregnancy using long-acting morphine: an 18-month prospective cohort study in northwestern Ontario. *Canadian Family Physician.* 61(2), e88-e95.

[96] Roberts S, Pies C. Complex calculations: how drug use during pregnancy becomes a barrier to prenatal care. Matern Child Health J 2011;15:333

[97] Elms, N., Link, K., Newman, A., & Brogly, S. B. (2018). Need for women-centered treatment for substance use disorders: results from focus group discussions. *Harm reduction journal*, *15*(1), 1-8.

[98] Elms, N., Link, K., Newman, A., & Brogly, S. B. (2018). Need for women-centered treatment for substance use disorders: results from focus group discussions. *Harm reduction journal*, *15*(1), 1-8.

[99] Kuo C, Schonbrun YC, Zlotnick C, Bates N, Todorova R, Kao JC, et al. A qualitative study of treatment needs among pregnant and postpartum women with substance use and depression. *Subst Use Misuse*. 2013;48(14):1498–508

[100] Peacock-Chambers, E., Paterno, M. T., Kiely, D., Fioroni, T., Byatt, N., & Friedmann, P. D. (2021). Engagement in perinatal outpatient services among women in recovery from opioid use disorders. *Substance abuse*, 42(4), 1022-1029.

[101] Holbrook BD. The effects of nicotine on human fetal development. *Birth Defects Res C Embryo Today.* 2016;108(2):181–192. doi: 10.1002/bdrc.21128

[102] Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: A systematic review based on 173 687 malformed cases and 11.7 million controls. *Hum Reprod Update*. 2011;17(5):589–604

[103] Jones HE, Heil SH, Tuten M, et al. Cigarette smoking in opioid-dependent pregnant women: Neonatal and maternal outcomes. *Drug and Alcohol Dependence.* 2013;131(3):271–277

[104] Mendelsohn CP, Gould GS, Oncken C. Management of smoking in pregnant women. *Aust Fam Physician*. 2014;43(1)

[105] Kandall SR, Akbin RS, Gartner LM, Lee KS, Eidelman A, Lowinson J, et al. The narcotic dependent mother: fetal and neonatal consequences. *Early Hum Develop.* 1977;1:159–169

[106] Dietz PM, England LJ, Shapiro-Mendoza CK, et al. Infant Morbidity and Mortality Attributable to Prenatal Smoking in the US. *Am J Prev Med.* 2010;39(1):45–52

[107] Pollack HA. Sudden infant death syndrome, maternal smoking during pregnancy, and the cost-effectiveness of smoking cessation intervention. *American journal of public health.* 2001;91(3):432–436

[108] Bowker K, Lewis S, Coleman T, Cooper S. Changes in the rate of nicotine metabolism across pregnancy: A longitudinal study. *Addiction*. 2015;110(11):1827–1832

[109] Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev*. 2018

[110] Diamanti, A., Papadakis, S., Schoretsaniti, S., Rovina, N., Vivilaki, V., Gratziou, C., & Katsaounou, P. A. (2019). Smoking cessation in pregnancy: An update for maternity care practitioners. *Tobacco induced diseases,* 17.

[111] Stotts AL, Northrup TF, Cinciripini PM, et al. Randomized, controlled pilot trial of bupropion for pregnant smokers: challenges and future directions. *Am J Perinatol.* 2015;32(4):351–356

[112] Richardson JL, Stephens S, Yates LM, et al. Pregnancy outcomes after maternal varenicline use; analysis of surveillance data collected by the European Network of Teratology Information Services. *Reprod Toxicol*. 2017;67:26–34

[113] Harter, K. (2019). Opioid use disorder in pregnancy. *Mental Health Clinician,* 9(6), 359-372

[114] Tsakiridis, I., Mamopoulos, A., Athanasiadis, A., & Dagklis, T. (2019). The management of nausea and vomiting of pregnancy: synthesis of national guidelines. *Obstetrical & Gynecological Survey*, 74(3), 161-169

[115] El Marroun H, et al. (2009) Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. *J Am Acad Child Adolesc Psychiatry*.;48(12):1173-1181. and (2018) An epidemiological, developmental and clinical overview of cannabis use during pregnancy. *Prev Med*.;116:1-5

[116] Richardson KA, Hester AK, McLemore GL. Prenatal cannabis exposure - The “first hit” to the endocannabinoid system. *Neurotoxicol Teratol*. 2016;58:5-14. doi:10.1016/j.ntt.2016.08.003

[117] Sorensen, C. J., DeSanto, K., Borgelt, L., Phillips, K. T., & Monte, A. A. (2017). Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology, and treatment—a systematic review. *Journal of Medical Toxicology*, 13(1), 71-87.

[118] Wallace, E. A., Andrews, S. E., Garmany, C. L., & Jelley, M. J. (2011). Cannabinoid hyperemesis syndrome: literature review and proposed diagnosis and treatment algorithm. *South Med J,* 104(9), 659-664

[119] Hutton, J. (2021). Distinguishing Cannabinoid Hyperemesis from Hyperemesis Gravidarum. *EC Gynaecology,* 10, 102-105.

[120] London, V et al. (2017). Hyperemesis gravidarum: a review of recent literature. *Pharmacology*, *100*(3-4), 161-171.

[121] Soens MA, He J, Bateman BT. Anesthesia considerations and post- operative pain management in pregnant women with chronic opi- oid use. *Semin Perinatol*. 2019;43(3):149-161

[122] Sen, S., Arulkumar, S., Cornett, E. M., Gayle, J. A., Flower, R. R., Fox, C. J., & Kaye, A. D. (2016). New pain management options for the surgical patient on methadone and buprenorphine. *Current pain and headache reports*, *20*(3), 1-8.

[123] Sunilkumar, M. M., & Lockman, K. (2018). Practical pharmacology of methadone: A long-acting opioid. *Indian Journal of Palliative Care*, *24*(Suppl 1), S10.

[124] Jones, H. E., O'Grady, K., Dahne, J., Johnson, R., Lemoine, L., Milio, L., ... & Selby, P. (2009). Management of acute postpartum pain in patients maintained on methadone or buprenorphine during pregnancy. *The American journal of drug and alcohol abuse*, *35*(3), 151-156.

[125] Meyer M, Wagner K, Benvenuto A, Plante D, Howard D Intrapartum and postpartum analgesia for women maintained on methadone during pregnancy. *Obstet Gynecol.* 2007 Aug; 110(2 Pt 1):261-6

[126] Dryden C, Young D, Hepburn M, et al. Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. *BJOG : an international journal of obstetrics and gynaecology.* 2009;116(5):665–671

[127] McQueen KA, et al. The impact of infant feeding method on neonatal abstinence scores of methadone-exposed infants. *Advances in neonatal care : official journal of the National Association of Neonatal Nurses.* 2011;11(4):282–290

[128] O'Connor AB, Collett A, Alto WA, et al. Breastfeeding Rates and the Relationship Between Breastfeeding and Neonatal Abstinence Syndrome in Women Maintained on Buprenorphine During Pregnancy. *J Midwifery Wom Heal.* 2013;58(4):383–388

[129] Academy of Breastfeeding Medicine Protocol C. Jansson LM. ABM clinical protocol #21: Guidelines for breastfeeding and the drug-dependent woman. *Breastfeeding medicine: the official journal of the Academy of Breastfeeding Medicine.* 2009;4(4):225–228

[130] Schwarz, E.B., Ray, R.M., Stuebe, A.M., Allison, M.A., Ness, R.B., Freiberg, M.S., et al. (2009). Duration of lactation and risk factors for maternal cardiovascular disease. *Obstetrics & Gynecology;* 113(5): 974-982.

[131] American College of Obstetricians and Gynecologists. (2013). Committee Opinion No. 570: Breastfeeding in Underserved Women: Increasing Initiation and Continuation of Breastfeeding.

[132] Ray, J. G., Park, A. L., Dzakpasu, S., Dayan, N., Deb-Rinker, P., Luo, W., & Joseph, K. S. (2018). Prevalence of severe maternal morbidity and factors associated with maternal mortality in Ontario, Canada. *JAMA network open*, *1*(7), e184571-e184571.

[133] Dzakpasu, et al (2019). Severe maternal morbidity in Canada: temporal trends and regional variations, 2003-2016. *Journal of Obstetrics and Gynaecology Canada*, *41*(11), 1589-1598

[134] Lisonkova, S., Richter, L. L., Ting, J., Muraca, G. M., Wen, Q., Mehrabadi, A., ... & Lyons, J. (2019). Neonatal abstinence syndrome and associated neonatal and maternal mortality and morbidity. *Pediatrics*, *144*(2)

[135] Murray L, Fiori-Cowley A, Hooper R, Cooper P The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. *Child Dev.* 1996 Oct; 67(5):2512-26.

[136] Klinger G, Selective serotonin reuptake inhibitor induced neonatal abstinence syndrome. *Isr J Psych Relat Sci*. 2008; 45(2):107-13.

[137] Stephansson O, et al Selective serotonin reuptake inhibitors during pregnancy and risk of stillbirth and infant mortality. *JAMA*. 2013 Jan 2; 309(1):48-54

[138] Perananthan V, Buckley NA. Opioids and antidepressants: which combinations to avoid. *Aust Prescr* 2021;44:41-4.

[139] Daoud, N et al (2019). Postpartum depression prevalence and risk factors among Indigenous, non-Indigenous and immigrant women in Canada. *Canadian Journal of Public Health*, *110*(4), 440-452.

[140] Benningfield MM, Arria AM, Kaltenbach K, et al. Co-occurring psychiatric symptoms are associated with increased psychological, social, and medical impairment in opioid dependent pregnant women. *Am J Addict.* 2010;19(5):416–421

[141] Gressier, F., Guillard, V., Cazas, O., Falissard, B., Glangeaud-Freudenthal, N. M., & Sutter-Dallay, A. L. (2017). Risk factors for suicide attempt in pregnancy and the post-partum period in women with serious mental illnesses. *Journal of Psychiatric Research*, *84*, 284-291

[142] Campbell, J., Matoff-Stepp, S., Velez, M. L., Cox, H. H., & Laughon, K. (2021). Pregnancy-associated deaths from homicide, suicide, and drug overdose: Review of research and the intersection with intimate partner violence. *Journal of Women's Health*, *30*(2), 236-244

[143] Nielsen, T., Bernson, D., Terplan, M., Wakeman, S. E., Yule, A. M., Mehta, P. K., ... & Schiff, D. M. (2020). Maternal and infant characteristics associated with maternal opioid overdose in the year following delivery. *Addiction*, *115*(2), 291-301.

[144] Alhusen, J. L., Ray, E., Sharps, P., & Bullock, L. (2015). Intimate partner violence during pregnancy: maternal and neonatal outcomes. *Journal of women's health*, *24*(1), 100-106.

[145] Stone, R., & Rothman, E. F. (2019). Opioid use and intimate partner violence: A systematic review. *Current Epidemiology Reports*, *6*(2), 215-230.

[146] Garbarino, J. (2001). Lost boys: Why our sons turn violent and how we can save them. *Smith College Studies in Social Work*, *71*(2), 167-181.

[147] Campbell, J et al. (2021). Pregnancy-associated deaths from homicide, suicide, and drug overdose: Review of research and the intersection with intimate partner violence. *Journal of Women's Health*, *30*(2), 236-244

[148] Campbell, J et al. (2021). Pregnancy-associated deaths from homicide, suicide, and drug overdose: review of research and the intersection with intimate partner violence. *Journal of Women's Health*, *30*(2), 236-244.

[149] Chen PH, Rovi S, Washington J, Jacobs A, Vega M, Pan KY, Johnson MS. Randomized comparison of 3 methods to screen for domestic violence in family practice. *Ann Fam Med.* 2007;Sep-Oct; 5(5):430-5.

[150] Bjork, J. M., & Grant, S. J. (2009). Does traumatic brain injury increase risk for substance abuse? *Journal of neurotrauma*, *26*(7), 1077-1082.

[151] Jeremy RJ, Bernstein VJ. Dyads at risk: Methadone-maintained women and their four-month-old infants. *Child Development.* 1984;55:1141–1154.

[152] Hans LL, Bernstein VJ, Henson LG. The role of psychopathology in the parenting of drug-dependent women. *Development and Psychopathology.* 1999;11:957–977.

[153] Hofkosh D, Pringle JL, Wald HP, Switala J, Hinderliter SA, Hamel SC. Early interactions between drug-involved mothers and infants: Within-group differences. *Archives of Pediatrics and Adolescent Medicine.* 1995;149:665–672

[154] Capen K (1997) Mother's Rights Can't be Infringed to protect fetus, Supreme Court's landmark ruling states. *Can Med Assoc J*;157:1586-7.

[155] Boyd, S. C., & Marcellus, L. (2007). *With Child: Substance use during pregnancy, A woman-centred approach*.

[156] Derkas, E. (2012). " Don't let your pregnancy get in the way of your drug addiction": CRACK and the ideological construction of addicted women. *Social Justice*, *38*(3 (125), 125-144.

[157] Paltrow, Lynn M. (Winter 2003). ""Why Caring Communities Must Oppose C.R.A.C.K./Project Prevention: How C.R.A.C.K. Promotes Dangerous Propaganda". (505 KB). *The Journal of Law in Society* (Wayne State University) **5** (11): 11–117.

[158] Krieg, B. (2016). Understanding the role of cultural continuity in reclaiming the identity of young Indigenous women. *Girlhood Studies*, *9*(2), 28-45.

[159] Dawe S, Harnett PH, Staiger P, Dadds MR Parent training skills and methadone maintenance: clinical opportunities and challenges. *Drug Alcohol Depend.* 2000 Jul 1; 60(1):1-11.

[160] Torresani S, Favaretto E, Zimmermann C Parental representations in drug-dependent patients and their parents. *Compr Psychiatry*. 2000 Mar-Apr; 41(2):123-9

[161] Cidro, J., Doenmez, C., Sinclair, S. et al. (2021). Putting them on a strong spiritual path: Indigenous doulas responding to the needs of Indigenous mothers and communities. *International journal for equity in health*, *20*(1), 1-11.

[162] Wiechelt, S. A., & Sales, E. (2001). The role of shame in women's recovery from alcoholism: The impact of childhood sexual abuse. *Journal of Social Work Practice in the Addictions*, *1*(4), 101-116.

[163] Sperlich, M., Seng, J. S., Li, Y., Taylor, J., & Bradbury-Jones, C. (2017). Integrating trauma-informed care into maternity care practice: conceptual and practical issues. *Journal of midwifery & women's health*, *62*(6), 661-672.

[164] Sanders, A. N., Vance, D. E., Dudding, K. M., Shorten, A., & Rice, M. (2022, January). Maternal-infant bonding for the opioid exposed dyad: A rodgers' evolutionary concept analysis. In *Nursing Forum* (Vol. 57, No. 1, pp. 165-170).

[165] Blackstock, C., Clarke, S., Cullen, J., D'Hondt, J., & Formsma, J. *Keeping the promise: The convention on the rights of the child and the lived experiences of first nations youth*. First Nations Child and Family Caring Society of Canada. 2004. https://fncaringsociety.com/sites/default/files/docs/KeepingThePromise.pdf

[166] Kenny, K. S., Barrington, C., & Green, S. L. (2015). I felt for a long time like everything beautiful in me had been taken out: Women's suffering, remembering, and survival following the loss of child custody. Int. *J. Drug Policy,* 26, 1158–1166.

[167] Marsh, W., & Leamon, J. (2019). Babies Removed at Birth: What Professionals Can Learn From 'Women Like Me'. *Child Abuse Review*, 28(1), 82–86

[168] Wall-Wieler, E et al (2018). Postpartum depression and anxiety among mothers whose child was placed in care of child protection services at birth: a retrospective cohort study. *Maternal and Child Health Journal*, *22*(10), 1393-1399.

[169] Thumath, M. et al. (2021). Overdose among mothers: The association between child removal and unintentional drug overdose in a longitudinal cohort of marginalised women in Canada. *International Journal of Drug Policy*, *91*, 102977.

[170] Malone KG. *Change to Manitoba's child apprehension laws ensures kids can't be taken solely because of poverty*. CBC News. Available from: https://www.cbc.ca/news/canada/manitoba/manitoba-cfs-child-apprehension-changes-1.4894953. 2019

[171] Blackstock, C. et al. (2006). *Reconciliation in child welfare: Touchstones of hope for indigenous children, youth, and families.* Ottawa, ON, Canada: First Nations Child & Family Caring Society of Canada/Portland OR: National Child Welfare Association.

[172] Larrieu, J. A. et al (2008). Predictors of permanent loss of custody for mothers of infants and toddlers in foster care. *Infant Mental Health Journal: Official Publication of The World Association for Infant Mental Health*, *29*(1), 48-60.

[173] Mackay, L., Ickowicz, S., Hayashi, K., & Abrahams, R. (2020). Rooming-in and loss of child custody: key factors in maternal overdose risk. *Addiction (Abingdon, England)*, *115*(9), 1786.

[174] Schiff DM, Nielsen T, Terplan M, et al. Fatal and Nonfatal Overdose Among Pregnant and Postpartum Women in Massachusetts. *Obstet Gynecol*. 2018;132:466–74

[175] Wright, T. G., Liu, W., Heideman, E., Kendle, A., Delgado, A., & Louis, J. (2022). The association between traumatic birth events and opioid relapse after delivery. *American Journal of Obstetrics & Gynecology*, *226*(1), S404-S405.

[176] Chapman SLC, Wu L-T. Postpartum substance use and depressive symptoms: a review. *Women Health*. 2013;53(5):479–503

[177] Schauberger, C. W., Borgert, A. J., & Bearwald, B. (2020). Continuation in treatment and maintenance of custody of newborns after delivery in women with opioid use disorder. *Journal of Addiction Medicine*, *14*(2), 119-125.

[178] Thumath M et al. Overdose among mothers: The association between child removal and unintentional drug overdose in a longitudinal cohort of marginalised women in Canada. *Int J Drug Policy*. 2020 Oct 28:102977.

[179] Gorski T, Miller M. *Staying Sober: A Guide for Relapse Prevention.* Independence, MO: Independence Press; 1986.

[180] Melemis, S. M. (2015). Focus: addiction: relapse prevention and the five rules of recovery. *The Yale journal of biology and medicine*, *88*(3), 325.

[181] Covington, E. C., et al. (2020, October). Ensuring patient protections when tapering opioids: consensus panel recommendations. In *Mayo Clinic Proceedings* (Vol. 95, No. 10, pp. 2155-2171). Elsevier.

[173] Boyd, S. C., & Marcellus, L. *With Child: Substance use during pregnancy, A woman-centred approach*. Fernwood Publishing. 2007.

[182] Ferri, M., Minozzi, S., Bo, A., & Amato, L. (2013). Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database of Systematic Reviews*, (6).

[183] Schneider C, Fischer G, Diamant K, et al. Pregnancy and Drug Dependence. Wien Klin Wochenschr 1996;108:611-4. 31. Etzersdorfer P, Fischer G, Eder H, et al. Comparison of morphine and methadone maintenance in pregnant opiate addicts. *NIDA Res Monogr*. 1997;178:343.

[184] Minozzi S, Amato L, Vecchi S, and Davoli M. Maintenance agonist treatments for opiate dependent pregnant women (Review). *The Cochrane Collaboration*. 2009; Issue 1: i-24.

[185] Towers, C. V., & Deisher, H. (2020). Subcutaneous extended-release buprenorphine use in pregnancy. *Case Reports in Obstetrics and Gynecology*, *2020*.

[186] Cleary, E. M., Byron, R. K., Hinely, K. A., Talley, A. W., Costantine, M. M., & Rood, K. M. (2020). Subcutaneous buprenorphine extended-release use among pregnant and postpartum women. *Obstetrics & Gynecology*, *136*(5), 902-903.

[187] Winhusen, T., Lofwall, M., Jones, H. E., Wilder, C., Lindblad, R., Schiff, D. M., ... & Rosa, C. (2020). Medication treatment for opioid use disorder in expectant mothers (MOMs): Design considerations for a pragmatic randomized trial comparing extended-release and daily buprenorphine formulations. *Contemporary Clinical Trials*, *93*, 106014.

[188] Bernstein, S. N., Peckham, A. M., Schiff, D. M., & Gray, J. R. (2021). Subcutaneous buprenorphine extended-release use among pregnant and postpartum women. *Obstetrics & Gynecology*, *137*(2), 377-378.

[189] Cleary, E. M., Byron, R. K., Hinely, K. A., Talley, A. W., Costantine, M. M., & Rood, K. M. (2020). Subcutaneous buprenorphine extended-release use among pregnant and postpartum women. *Obstetrics & Gynecology*, *136*(5), 902-903.