Opioid Agonist Therapy 101:
An Introduction to Clinical Practice Workshop

ASSESSING AND TREATING OPIOID USE DISORDER IN PREGNANCY

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Faculty/Presenter Disclosure

- **Faculty:** Marina Reinecke
- **Relationships with commercial interests:** None

LEARNING OBJECTIVES

At the end of this educational activity, the participant will be able to:

- Discuss evidence based care for opioid use disorder in pregnancy.
- Discuss best practices related to managing pain and opioid withdrawal during labor and immediately postpartum in women with opioid use disorder.
- Discuss best practices for managing opioid withdrawal in the infant and how this relates to caring for the mom

SCREENING FOR OPIOID USE DISORDER

- There is **no** simple screening tool for women with opioid use disorder
- A **detailed assessment** is required when opioid use disorder is suspected in pregnancy
- **All** pregnant women should be asked about current or past history of alcohol, tobacco, Rx and illicit drug use – **Universal screening!**

ASSESSMENT FOR OPIOID USE DISORDER

- **Withdrawal symptoms**: diaphoresis (sweating), runny nose, runny eyes, nausea, vomiting ,diarrhea, myalgias (muscle pains), **remember if women is in withdrawal, the fetus is too!**
- **Chronic pain**: diagnosis, response to pain rating scale (dramatic or inconsistent), functional status, pain related to previous obstetrical events (epidurals, pelvic injuries)
- **Physical/sexual abuse**: past hx - and **present risk**, ask repeatedly, safety plan, numbers for shelters and how to get there
- **Psychosocial assessment**: marital status, living arrangements, parenting arrangements, safety of children in home

WOMEN….

- Often introduced to opiates by male partner
- Frightened of withdrawal - Must find $60-$70 /day x 7 days/wk (approx. $25,000/yr)
- The result: Survival sex (using sex to pay for her drugs)
- Unplanned pregnancy, multiple pregnancy terminations/associated trauma, substance using women are **POOR** users of fertility control
- When pregnant: poor nutrition, escalation of domestic violence, increased stress levels, lack of prenatal care, poor support
- Time of heightened motivation to make changes

RISKS OF OPIOID USE DISORDER IN PREGNANCY

- Opioid use disorder during pregnancy has been associated with numerous adverse fetal outcomes secondary to the drug itself, as well as, secondary to poor nutrition and inadequate prenatal care

- Poor neonatal outcomes such as:
  1. Intrauterine growth restriction
  2. Lower birth weight
  3. Preterm rupture of membranes

RISKS OF OPIOID USE DISORDER

- Opioid withdrawal can trigger uterine contractions leading to an increased risk of **spontaneous abortion (miscarriage)** in the first trimester, **premature labor** in the third trimester

- Maternal complications include **pre-eclampsia** (pregnancy related high blood pressure) and **antenatal bleeding**

- Heroin can lead to intrauterine growth restriction

OPIOID WITHDRAWAL SYMPTOMS

Psychological

- Intense anxiety, agitation
- Intense craving for opiates
- Restlessness, insomnia, fatigue

Physical

In pregnancy: uterine irritability and a fetus at risk

- Muscle aches, flu-like symptoms “dope sick”
- Nausea, vomiting, cramps, diarrhea
- Sweating, goose bumps
- Dilated pupils
- Runny eyes

ABSTINENCE-BASED TREATMENT IN PREGNANCY

- Medical detoxification
  - Opioid tapering - **Not recommended** - due to **fetal risk** and **poor success rates** – however support women's choice & go slow!
  - Could consider if using low doses and done very slowly
  - **Note: Clonidine contraindicated in pregnancy!**
- NA, AA, self-help groups
- Residential or outpatient treatment
- Success requires major life changes/good supports

OPIOID AGONIST THERAPY (methadone or buprenorphine)[1]

- **Present standard of care for opioid use disorder in pregnancy is methadone maintenance therapy (MMT)**
- Can be initiated in hospital or in an outpatient setting
- Women on methadone are less likely to experience withdrawal symptoms and drug cravings
- Methadone-maintained pregnancies have **reduced obstetrical complications and improved outcomes**
- Ideally, prescribed in the context of comprehensive pregnancy care, including:

Counselling	**Housing**
Family therapy	**Food support**
Parenting planning	**Medical care**

Cont'd

LIMITATIONS OF METHADONE

- High risk of overdose early in treatment
- Not all communities have methadone providers **(despite being the standard of care)**
- Major commitment of time for woman – very difficult for woman with children to attend daily
- Transport issues
- Woman's family/partner/other health care providers/CFS may NOT be supportive – "exchanging one drug for another"
- Some treatment agencies in MB has intake criteria not motivated by medical evidence

METHADONE TAPERING

- Some women want to decrease their dose so their baby won't experience withdrawal - preliminary studies of methadone tapering during pregnancy documenting no adverse outcomes (if done slowly)
- Taper **slowly to avoid distress or labour**
- In reality tapers poorly tolerated, can be destabilizing
- Some women require a dose increase in pregnancy – offer a pregnancy test if a patient stable on MMT requires an increased dose

NON-STRESS TESTING & METHADONE

- Normal, reassuring, result depends on intact well oxygenated, non-sedated brain acting on a normal heart
- Fetus may have decreased movement in utero for two to four hours after a methadone dose
- It is important to repeat testing after the peak level of methadone has been reached
- Standard practice is to perform more frequent fetal testing after 32 weeks **in any patient with maternal or fetal risk factors**

NON-STRESS TESTING & METHADONE

- Narcotics **alone** are **not** an indication for a NST; order NST for obstetrical reasons
- Monitoring using a combination of BPP (biophysical profile and NST) after 32 weeks may be helpful
- If NST is indicated, consider methadone or other narcotic in interpretation

BUPRENORPHINE FOR OPIOID USE DISORDER

- Sublingual partial agonist, effective +/- 80 mg of methadone; far safer than methadone (ceiling effect)
- Buprenorphine is safe in pregnancy (speculation regarding effect on neurodevelopment of the fetus – minimal data from small studies)
- If a woman is on buprenorphine (Subutex®) prior to pregnancy she can stay on the same treatment
- Historically: Women on buprenorphine/naloxone (Suboxone®) were advised to transfer to buprenorphine alone product (Subutex®) due to unknown safety of naloxone in pregnancy

BUPRENORPHINE

- However, buprenorphine (Subutex®) is not marketed in Canada and could only be accessed through Health Canada's special access program for specific clinical situations (pregnancy and allergy to naloxone)
- Took weeks….
- MB methadone and buprenorphine maintenance Recommended Practice document acknowledges this difficulty and states that pregnant patients often remain on Suboxone® in 2014/2015

BUPRENORPHINE

- **Re naloxone concern:**
- Teratogenicity based on a rat model
- Never actually shown in humans
- Vey low bioavailability with proper sublingual administration
- Gestation matters
- Handful studies with small sample sizes that documented no adverse maternal or fetal outcomes with the combo product; better outcomes for withdrawal as compared to methadone

Buprenorphine studies in pregnancy

- 1: Wiegand SL, Stringer EM, Stuebe AM, Jones H, Seashore C, Thorp J. Buprenorphine and naloxone compared with methadone treatment in pregnancy. Obstet Gynecol. 2015 Feb;125(2):363-8. doi: 10.1097/AOG.0000000000000640. PubMed PMID: 25569005.

- 2: Soyka M. Buprenorphine use in pregnant opioid users: a critical review. CNS Drugs. 2013 Aug;27(8):653-62. doi: 10.1007/s40263-013-0072-z. Review. PubMed PMID: 23775478.

- 3: Debelak K, Morrone WR, O'Grady KE, Jones HE. Buprenorphine + naloxone in the treatment of opioid dependence during pregnancy-initial patient care and outcome data. Am J Addict. 2013 May-Jun;22(3):252-4. doi: 10.1111/j.1521-0391.2012.12005.x. PubMed PMID: 23617867.

- 4: Lund IO, Fischer G, Welle-Strand GK, O'Grady KE, Debelak K, Morrone WR, Jones HE. A Comparison of Buprenorphine + Naloxone to Buprenorphine and Methadone in the Treatment of Opioid Dependence during Pregnancy: Maternal and Neonatal Outcomes. Subst Abuse. 2013;7:61-74. doi: 10.4137/SART.S10955. Epub 2013 Mar 14. PubMed PMID: 23531704; PubMed Central PMCID: PMC3603528.

Since then….

- Health Canada has removed it's recommendation that patients need to be switched over!
- Risk-benefit discussion, then Rx…..

The case for opioids other than methadone/buprenorphine…..

- She doesn't want it despite intensive education
- No access
- An ethical crisis…

Pregnant women deserve special consideration…

- **Other opioids are effective:**
- Cochrane review; Little difference in newborn or maternal outcomes for pregnant opiate-dependent women who were maintained on methadone, buprenorphine, or oral slow release morphine (Minozzi et al, 2009)
- Proceed with caution! **OFF Label**
- Document, document, document….
- Treatment agreement
- Daily dispensing
- Long acting morphine
- Lowest functional dose with frequent follow - up

URINE DRUG SCREENS

- If urine drug screening is required as part of MMT, in hospital or by protection services, it must be with **maternal consent**

- If there has been maternal drug use, and there are significant medical concerns for the neonate and the mother is unable or unwilling to give consent, then drug screens on neonate may be taken without consent

- **Note: An unexpected positive result merits confirmatory testing!** **(same sample if possible)**

ROLE OF UDS:
Child Protection Services

- Women involved with Child Protection Services often want to have regular UDS
- UDS provide objective evidence to CFS, to care providers and to the patient's families that they are not using illicit drugs
- In some cases, CFS insist on UDS as a condition for custody
- Such UDS's needs to be collected with chain of custody by certified lab

UDS:
New Patients in Labour

- The mother should be asked about substance use and offered treatment and follow up

- The baby should be monitored for neonatal withdrawal if:

  - The mother reports opioid use
  - The baby's UDS is positive for opioids
  - The baby shows signs of withdrawal
  - Withdrawal presentation similar to other conditions e.g., sepsis, hypoglycemia, hypocalcemia

PAIN MANAGEMENT IN LABOUR

What can affect a woman's pain?

Personal factors

- Past negative experience
- Sexual abuse history
- Fear, anxiety
- Cultural perspective
- Tolerance

Labor: Occiput Posterior position

- Previous pelvic fracture

Hospital factors

- Lack of support
- Unwanted support
- Loss of control
- Hypervigilence
- Lack of privacy
- Harsh behaviour by staff

LABOUR & DELIVERY

- Labour hurts
- Analgesia must be offered to all women in labour
- Methadone alone is **NOT** adequate or appropriate analgesia for labour
- Epidural is good, particularly advantageous with methadone

LABOUR & DELIVERY ISSUES

- Adequate analgesia: opioid-dependent women may require larger doses of analgesics - it will not worsen addiction
- Injection drug users may have poor IV access - planned IV access is recommended
- Methadone dose should be maintained during labour-some women will need a reduction in methadone dose postpartum
- If not on methadone, can use morphine for the management of withdrawal

RISKS OF MMT FOR INFANT

- Only risk of methadone in pregnancy is the risk of neonatal withdrawal (NW)
- Meta-analysis data indicate 60-80% of infants experience mild NW
- A smaller percentage (~ 30%) require morphine treatment for significant withdrawal symptoms
- Most infants will respond to comfort measures
- No evidence of any long-term consequences associated with methadone use in pregnancy
- Increased occurrence of strabismus in infants born to women receiving methadone

NEONATAL WITHDRAWAL

- Now believed to be related to methadone dose (to some degree)
- Other **major** factors impacting severity of withdrawal and need for morphine treatment:
  - Rooming in
  - Breastfeeding
  - Mom on multiple medications associated with withdrawal
  - Staff and Centre practices and attitudes
- NICU admissions very costly; so are apprehensions
- Occurs 2-4 days after birth, can last a couple of weeks

NEONATAL WITHDRAWAL

- Poor feeding, irritability, mottled skin, crying, jitteriness, inability to gain weight
- If rooming in and promoting breast feeding, comfort measures usually sufficient, morphine may be necessary
- Remember to look for other serious problems: sepsis, hypoglycemia, etc. in an unstable infant - do not assume signs due to neonatal withdrawal
- Suggest neonatology/pediatrics consult in hospital with at least Level II capabilities if infant is unstable

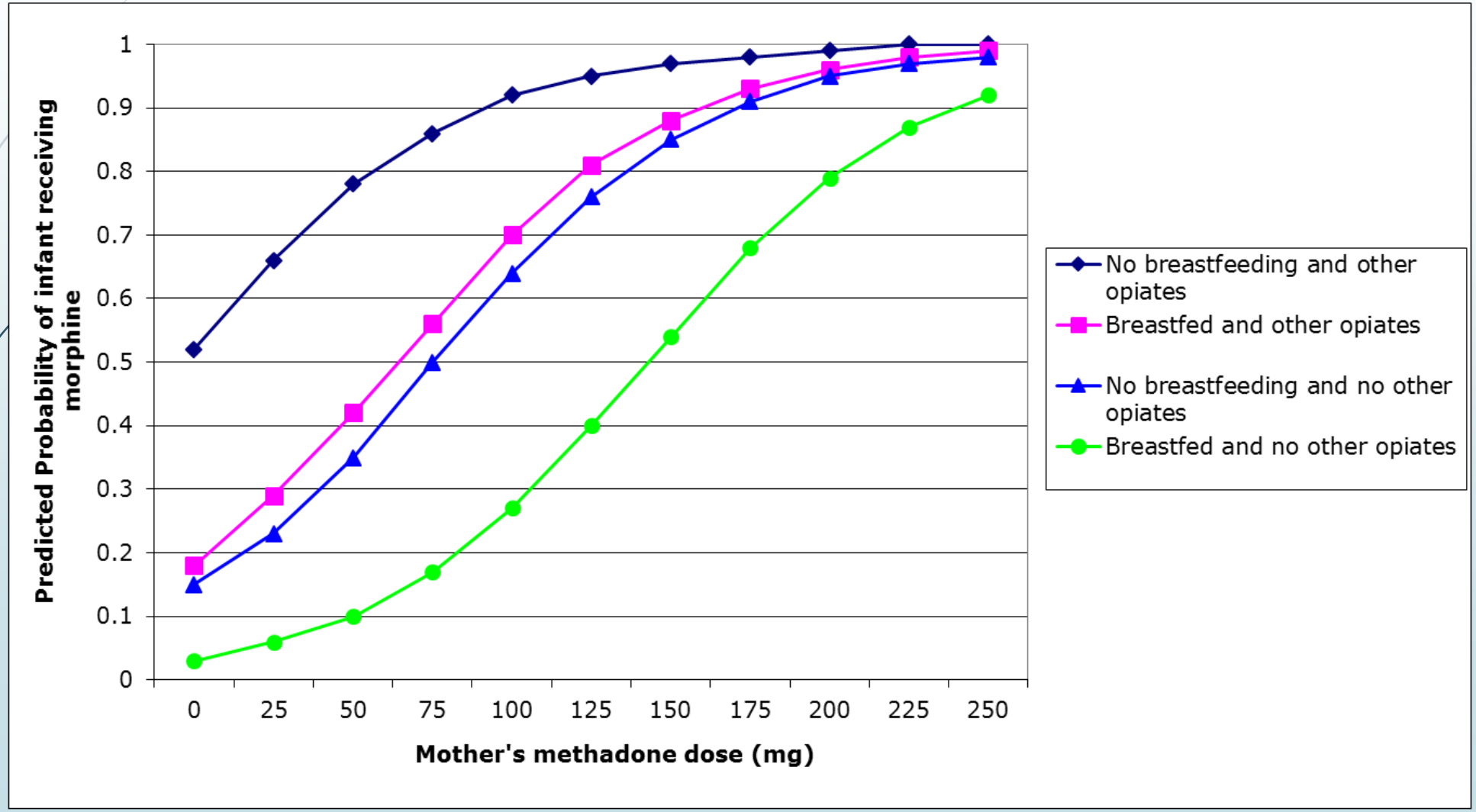
An Evaluation of Rooming-in Amongst Substance-Exposed Newborns in British Columbia
R. Abrahams et al SEPT JOGC, 2010

- Retrospective comparison of Rooming-in (n=371) vs. Standard care (n=834) using BC Perinatal Heath Program Data.

- Rooming-in associated with:
  - Significant decrease in admissions to NICU
  - Increased likelihood of breastfeeding during hospital stay
  - Increased odds of baby being discharged home with his/her mother

- **Review supports the finding that rooming-in is both safe and beneficial for substance-exposed babies.**

Probability Methadone/Morphine Tx JOGC, May, 2011



BREASTFEEDING

- Methadone enters breast milk in very small quantities
- Safe to breastfeed on methadone and buprenorphine regardless of dose (Suboxone included)
- Ensure close follow-up of mother and baby
- **Rooming-in** is the best option to encourage attachment and development of parenting skills
- If baby needs to go to the nursery, parents should accompany and be encouraged to hold and cuddle infant 24/7 if possible

Health Canada Santé Canada

Aug 2nd, 2018

Summary Safety Review – METHADOSE and METADOL-D - Assessing the potential risk of serious harm in children exposed to methadone through breast milk

Product: Methadose, Metadol-D (methadone hydrochloride)

Potential Safety Issue: Risk of serious harm (including death) in children breastfed by mothers in methadone treatment

Key Messages

- Methadose and Metadol-D are methadone-containing drugs used to treat addiction to opioids (such as heroin) in adults. They work to prevent withdrawal symptoms, which are side effects caused by stopping the use of other opioids.
- Health Canada became aware of a published article[1] that reported 2 Canadian cases of death in children who had increased levels of methadone in their blood because they were being breastfed by mothers in treatment programs for opioid addiction (methadone maintenance programs).
- Health Canada's review of the available information found that there may be a link between methadone and the risk of serious harm (including death) in children exposed through breast milk. Health Canada will be working with the manufacturers of Methadose and Metadol-D to strengthen the existing product information to specifically include the risk of serious harm, including death, in children exposed to methadone through breast milk.

From a co-author…

“I am disappointed in their review of the two Canadian cases. The conclusions of these two cases (of which I am a co-author) were that numerous factors were at play including genetic predisposition (I have had my suspicions about CYP2B6 and NAS for a while), concomitant substance use and unsafe sleeping conditions. In both of these cases the cause of death was unascertained, but I cannot comment on the international cases that were reviewed”.

A direct quote from the two Canadian cases (attached). ”It would be inappropriate to assume that the methadone concentrations presented in this study are indicators of cause of death in these infants”.

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Breastfeeding and Methadone

"FDA (US) continues to monitor adverse events to infants who receive exposure to methadone via breastmilk.
Current FDA-approved methadone labeling acknowledges low levels of methadone in breast milk based on results of two clinical lactation studies in 22 women.
Further, due to case reports, our product labeling recommends prescribers to advise breastfeeding women to monitor the infant for increased drowsiness, difficulty breastfeeding, breathing difficulties or limpness.
Labeling includes documentation of rare cases of sedation and respiratory depression in infants exposed to methadone through breast milk".

U.S. clinical guidelines[1,2,3,4] encourage breastfeeding by mothers who are stable on methadone unless there are other contraindications such as human immunodeficiency virus (HIV) infection or use of illicit drugs.

NM
Pharmacist
Division of Drug Information
Center for Drug Evaluation and Research
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Breastfeeding and Methadone

Clinical Guidance for Treating Pregnant and Parenting Women With Opioid Use Disorder and Their Infants

Factsheet#11- BREASTFEEDING CONSIDERATIONS FOR INFANTS AT RISK FOR NEONATAL ABSTINENCE SYNDROME
https://store.samhsa.gov/product/Clinical-Guidance-for-Treating-Pregnant-and-Parenting-Women-With-Opioid-Use-Disorder-and-Their-Infants/SMA18-5054:
Substance Abuse and Mental Health Services Administration; January 2018.

Handout (Factsheet # 11)

POSTPARTUM CARE

- Assess social support, ensure community supports in place before discharge
- Mother may feel need to reduce amount of methadone within a few days of birth
- Ensure safety, food, shelter, baby supplies
- Regular ongoing support by stable team of caregivers is best predictor of good outcome
- Link parents to community supports and parenting resources

CHILD PROTECTION CONCERNS

- In Canada, the fetus is not a person; caregiver must only speak to child protection services IF a child, not a fetus, is unsafe.
- “Anyone who has reasonable grounds to suspect that a child may be in need of protection must make a report directly to Child Protection Services.”
- Speak to the mother first; ideally, she would call the CPS herself, requesting support be put in place prior to delivery
- **Self-report** prenatally increases self-efficacy, dignity, & stability while promoting optimal relations with child protection authorities.

Questions??

Further References

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