Title: The Effects of Opioids on Female Reproductive Health Across the Life Course

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Word Count: 3263

Declarations of interest: None

Abstract

Opioids cover a broad class of natural, synthetic and semi-synthetic drugs which act on opioid receptors within the central and peripheral nervous system to produce powerful analgesic effects. This includes illicit opioid use (e.g., heroin) and use which is associated with opioid agonist maintenance treatment (e.g., methadone or buprenorphine/naloxone). The rate of long-term opioid use has increased substantially in recent years, particularly among women. In Canada, opioid misuse is now a leading cause of death and other adverse effects. Data on the association with female health across the life course has not been well-described. The purpose of this review is to provide an overview of the literature on trends in use of opioids among females aged 15 years and older in relation to fertility, pregnancy, breastfeeding, and health in older ages. We searched the medical literature between August 2018 and August 2019 to look for studies related to health implications for opioid use among women. Outcomes included associations with fertility, pregnancy-related complications, breastfeeding, and older age outcomes.

Keywords (4-6): opioids, substance use, pregnancy, fertility, breastfeeding, women

Introduction

Increases in the prescription of potent opioid medications to treat chronic pain have resulted in an epidemic of drug overdose deaths in the United States and Canada.[1] Opioids are highly addictive and can cause dependence.[2] It is estimated that opioid-related misuse has contributed to the hospitalization or death of thousands of Canadians.[3–6] In the past decade, rates of hospitalizations related to opioid overdoses have increased by more than 50% from 10.2 to 15.6 per 100,000, with the majority of this increase occurring in the past three years.[3] In 2016, there were an estimated 2,861 opioid-related deaths in Canada making it one of the Country’s leading causes of death (more than motor vehicle accidents).[4,5] In addition, there has been documented increases in the number of individuals seeking addiction treatment for prescription opioids in Canada over the past two decades.[7]

The term ‘opioid’ refers to the natural derivatives of the opium poppy, as well as endogenous and synthetic compounds. The principal action of opioids is pain relief but euphoria and dissociation also occur, prompting recreational use. Each opioid has a different pattern of affinity for each of the three classical opioid receptors (mu, kappa and delta), either in an agonist or inhibitor role. Physical tolerance develops in chronic users, requiring higher doses to achieve the same degree of pain relief. With regular exposure, noradrenaline release is upregulated; when the supply of opioid ceases abruptly, overproduction of noradrenaline produces the constellation of signs and symptoms typical of withdrawal.

There are corresponding increasing rates of opioid use in pregnancy,[8–11] with increasing maternal morbidity and mortality. As a result, neonatal abstinence syndrome (NAS) or withdraw in newborns and associated complications have increased five-fold since 2000.[12] Use of opioids may lead to addiction and dependence. Opioid agonist maintenance treatment

(OAMT) with methadone or buprenorphine (combination or monoprodut) for opioid use disorder may reduce complications in pregnancy associated with withdrawal; methadone is a long-acting competitive mu-receptor agonist, while buprenorphine is a partial mu-opioid receptor agonist.[2]

There is a paucity of information regarding the effect of opioid use on female health across the life span, outside of pregnancy. This review focuses on the effects of opioids using a broad definition of use including illicit/prescription and natural/synthetic opioids on female fertility, pregnancy, breastfeeding, and in older age.

Methods

We assessed the published literature for studies related to opioid use among women with outcomes related to fertility, during pregnancy, breastfeeding, and in older age. Markers of opioid exposure included self-reported use and diagnoses of neonatal abstinence syndrome in infants, separate from the use of antidepressant medications known to have a risk of NAS.

To identify relevant papers a search was designed and carried in PubMed and the Cochrane Library databases from August 2018 until August 2019 with a focus on opioids/illicit drugs and fertility, pregnancy, breastfeeding, and aging. We supplemented the electronic search with relevant articles from the reference lists of identified articles.

Opioids and female reproductive health

Fertility

In women, opioids can impair endocrine function and sex steroid balance.[13] Opioids act on receptor sites and differentially stimulate or inhibit hormone release. These effects may

vary according to acute or prolonged exposure. Long-term opioid use has been shown to be associated with hypogonadism (a diminished function of the gonads, affecting production of sex hormones).[14] Studies in this area have focused on the relationship between endocrinopathy and prescribed oral opioids in men, although some papers were identified with a focus on women.[13–17] Daniell examined hormone levels for testosterone, estradiol, and dehydroepiandrosterone (DHEAS), among 47 women (aged 30-75 years) taking long-term oral or transdermal opioids, compared to 68 non-opioid using controls in an unmatched design.[16] Among opioid users, more than half of women aged 30-50 years experienced amenorrhea compared with 20% of controls ($P < 0.05$). Half of the women developed amenorrhea after initial opioid use; the remainder developed amenorrhea after opioid dose increases. Opioid users had hormone levels compared to controls that averaged 30% lower in premenopausal and 70% lower in postmenopausal age groups ($P < 0.001$). Rhodin *et al.* compared 39 women treated with opioids for a least one year to 20 non-opioid using controls, matched for age, pain duration, and type of pain.[17] Women under 50 years of age were found to have reduced estradiol, reduced levels of DHEAS, and reduced luteinizing hormone. Additionally, two of the sixteen women taking long-term opioids had regular menses, while all six of the women in the control group had normal menses.

Reduced libido and hypogonadism have been reported as consequences of chronic opioid use.[17–19] Abs *et al.* employed a prospective study of endocrine parameters and menses among 44 women with long-term use of intrathecal opioids compared to 9 controls; among premenopausal women receiving intrathecal opioids ($n=21$), all developed amenorrhea or had irregular menses. Compared with controls, serum luteinizing hormone, progesterone, and estradiol were significantly lower among women taking opioids.[15] Merza *et al.* questioned

whether associations in reduced hormonal function were related to oral opioids or comorbidities including obesity (n=37),[20] highlighting issues related to confounding and other potential biases in these studies. Although the literature suggests an association between long-term use of opioids and endocrine dysfunction related to amenorrhea and fertility in women, the studies are limited and no recent papers have been identified.

Pregnancy and Neonatal Risks

With the opioid epidemic in North America, opioid use and misuse in pregnancy has increased in the United States and Canada;[8–11] and has been shown to be related to opioid prescribing practices, particularly in the United States. Data between 2008 and 2018 suggest that up to one-third of reproductive-age women receive at least one prescription for an opioid medication annually.[21] Rates of use of illicit opioids such as heroin have also increased over the period from 2002 to 2013.[22] Increasing rates of opioid use in pregnancy are of a public health concern due to implications to the long-term health of users and exposed children.

Maternal substance use may present medical, legal, and economic consequences for the mother.[23] Women may have to be away from their home supports to accessing care and resources for NAS monitoring and treatment. Delivery and newborn care may need to be accessed in other centres, and this could cause financial hardship. There are postpartum and post-operative challenges with analgesia/anesthesia among women with a history of opioid use, and often these women are of lower socioeconomic status and have co-morbidities such as HIV or Hepatitis C.[24]

In Ontario, there has been a 16-fold increase in the number of infants born to opioid-dependent women, with rates increasing from 46 per year in 2002 to nearly 800 per year in

2014.[25] In other parts of Canada, data suggest that maternal drug and substance use including opioids has increased in pregnancy.[26] The incidence of NAS, occurring in the majority of newborns exposed to opioids in utero,[27–29] has risen dramatically over the past two decades, reflecting rapid increases in maternal prenatal use.[30–32] A population-based study from Ontario found that the incidence of NAS has increased 20-fold, from 0.28 per 1000 live births in 1992 to 4.29 per 1000 live births in 2011.[33]

In addition to NAS and its systemic complications, intrauterine exposure to opioids (either non-prescribed opioids or OAMT) is associated with a reduction in birth weight of 480 grams, on average,[34,35] and increased rates of small for gestational age status,[36,37] cardiovascular and neural tube defects (NTD),[38,39] and club foot,[40] although uncertainty remains regarding the teratogenicity of opioid use.[41] Although we consider non-prescribed and OAMT together, the socio-demographic and medical/mental health profile of women on chronic prescription opioids vs OMT are very similar.

Large retrospective studies from Sweden and Denmark examining neonatal outcomes in about 800 infants with prenatal exposure to buprenorphine, methadone, and other opioids found a higher than two-fold increase in the frequency of preterm birth, compared to non-exposed pregnancies.[37,42] Other studies have reported associations between prenatal opioid use and reduced head circumference[43] and sudden infant death compared to infants without prenatal exposure.[44] Further, two studies by the Centres for Disease Control in the United States have linked self-reported opioid medication use in pregnancy to birth defects including congenital heart defects, neural tube defects, and gastroschisis for women who took opioids pre-conception and in the first trimester;[38,39] these data were derived from the National Birth Defects Prevention Study, a population-based case-control study that examined 30 major structural

congenital anomalies. Sociodemographic (maternal age, race, education, study centre/region) and clinical factors (body mass index, gestational diabetes, smoking in pregnancy, use of prenatal vitamins) were considered although only study centre was included in the final model. A systematic review examined 68 studies related to prenatal opioid use and congenital disabilities; in 17 heterogeneous (10/12 case-control and 7/18 cohort) studies, they showed statistically significant associations with birth defects and malformations, including oral clefts and ventricular/atrial septal defects and club foot.[41] The authors had important concerns regarding the quality of the studies, high risk of bias, and the lack of generalizability and comparison groups.

In addition to comprehensive prenatal care and psychosocial interventions, opiate substitution therapy using long-acting opioid agonist medications, such as methadone and buprenorphine, is the standard of care for opioid-dependent women during pregnancy. It is associated with longer adherence to treatment and decreased risk of relapse, and with improved safety compared with continued non-medical opioid use during pregnancy, including improved prenatal care, longer gestation, higher birth weight, and increased rates of infants discharged home in the care of their mothers.[45]

The potential longer-term developmental effects in children with *in utero* exposure is unclear.[46,47] Several previous studies have suggested that children with prenatal exposure to opioids score lower on mental development and intelligence,[48–52] although other studies have been inconclusive.[53–56] Understanding of the associations between perinatal opioid exposure and offspring neurodevelopmental outcomes remains incomplete. The existing studies, although well-conducted, have limitations including choice of comparison groups, small sample sizes (most contain fewer than 80 exposed children), limited adjustment for confounding factors

(including maternal socioeconomic status, pre-existing mental health conditions, concurrent use of tobacco, alcohol, or other substances), reliance on self-reports of opioid exposure (which may be under-reported and subject to recall bias), limited duration of follow-up in children, lack access to large population-based samples, and studies which were conducted prior to recent increases in prenatal opioid use and use of OAMT.[48,49,51–58] More evidence and research is needed on the long-term sequelae and neurodevelopment of children exposed to opioids.

Breastfeeding

The WHO recommends breastfeeding in infants worldwide for optimal growth and development. The WHO further recommends that infants be exclusively breastfed for six months, and a systematic review indicated that those infants experience less morbidity and no differences in growth compared to partially-breastfed infants.[59] However, women may be advised to forgo or delay breastfeeding for a period when using certain medications or substances.[60] A recent review on this topic examined the literature related to breastfeeding and/or fed breast milk among women using opioids, those with opioid use disorder, and implications for neonatal abstinence syndrome in infants, and showed that newborns had less severe opioid withdrawal symptoms, shorter hospital stays, and were less likely to be treated with medication for withdrawal. The review clarified that these outcomes may be related to the act of breastfeeding and associated skin-to-skin contact, qualities of breastmilk, healthier microbiome, small amounts of opioid drug in breastmilk, and acknowledged the significant obstacles to breastfeeding, including psychosocial, behavioral, concomitant medications, and tobacco use.[60] Other research suggests that the primary motivators and barriers for breastfeeding are similar between women using opioids and opioid use disorder compared to the

general population.[61] Specific concerns for women using opioids were the potential for the transfer of medication and substances to the infant and concerns about milk supply. Opioid medications may be prescribed postpartum for pain management, and should be reviewed regularly to optimize pain management and assess ongoing requirement.[14] Pharmacokinetic data suggest that opioid medications can concentrate in breastmilk; this may vary depending on characteristics of the drug.[62] If the rate of clearance of the drug is high, the exposure to infants is generally low, even in breastmilk with a high drug concentration. For most drugs, the minimally effective clinical dose is not established; however, an arbitrary cut off of 10 percent of the therapeutic dose in infants is used as an arbitrary safety value (relative infant dose).[63] A relative infant dose received through breastmilk less than 10 percent of the therapeutic dose is usually considered clinically unimportant. A study of the pharmacokinetic properties of breastmilk from 30 mothers using opioids showed that, on average, fully breastfed newborns received 1.6% of the maternal dose for hydrocodone; the total median opioid dosage was 0.7% of the therapeutic level for infants.[64] A more recent review of pharmacokinetic data on opioid excretion in breastmilk considered several opioids for pain management (e.g., morphine, codeine, oxycodone, tramadol, fentanyl), and opioid dependence treatment (e.g., methadone, buprenorphine).[63] Most studies indicated that the relative infant dose was between <0.5% to 3%. A study on methadone indicated that the range of relative infant dose may be higher compared to other opioids (5-6%),[65] however this may contribute to the alleviation of symptoms related to NAS. In-patient newborn monitoring requires longer lengths of stay to evaluate for the need for pharmacologic management of NAS.

Studies have shown that both breastfeeding and the associated skin-to-skin contact may benefit the newborn by reducing pain and stress levels.[58,66] Frequent breastfeeding and infant-

led breastfeeding and comfort nursing may be beneficial for NAS symptoms and given increased caloric requirements in NAS infants. Several small studies have suggested lower rates of treatment for NAS among breastfed infants, and better in-hospital outcomes.[58,60,67–69] Small quantities of drugs such as methadone in breastmilk may also play a role for reducing withdrawal symptoms in infants.[60,70]

There may be challenges to establishing breastfeeding in infants with prenatal exposure to opioids. *In utero* exposure may negatively impact the development of swallowing and respiratory centres, leading to a dysregulation in patterns of feeding and sucking.[71] Women with opioid use disorders face other obstacles to breastfeeding compared to other women including social stigma, inconsistent advice from health care providers, mental health issues and other barriers.[72] Rooming-in of infants with mothers has also been shown to reduce barriers to breastfeeding, and establishing optimal rates of breastfeeding in this population may have considerable benefits.[72] Studies also suggest that rooming-in, may help reduce the incidence and severity of NAS among opioid-exposed infants,[73] need for pharmacologic treatment and length of hospital stay, compared to standard nursery care.[74]

Older Age

The effects of opioid use on health may vary across the life course. In older ages, women may experience persistent pain at rates as high as 50%-84% of the institutionalized population.[75] Persistent pain is also associated with reduced functional abilities and depressed mood, and opioid therapy may be prescribed in these women for pain management. Older women, however, may be at higher risk for adverse consequences associated with opioids, including respiratory depression, sedation, cognitive effects, and interaction with other drug

medications.[10] In addition, 40-60% of patients receiving opioids may experience opioid-induced constipation,[76] with older females at greater risk.[77]

In the older population, including among women, the long-term implications of opioid use on safety, efficacy, and potential for abuse and misuse are not well-understood.[78] Among older adults with chronic pain but no other comorbidities, short-term use of opioids may reduce pain intensity and improve physical functioning, but may negatively influence mental health functioning. One large prospective study of more than 10,000 nursing home residents (~88% female) with persistent pain analyzed outcomes according to classes of medication including short-acting (18.9%) and long-acting opioids (3.3%). The authors did not find any significant associations with cognitive status or depression among opioid users compared to non-users and rates of other adverse events were not increased, including falls.[75] Although this study did not present sex-stratified results, the majority of participants were female.

Other studies suggest that falls and fracture risk may be increased among older women taking opioids.[79,80] Saunders et al. examined a population of 60 years of age and older (mean age 73 years, 66% female) and showed a graded association between dose of opioid and likelihood of fracture, with 50 mg/day of opioids, the hazard ratio for fracture was 2.0 (95% CI: 1.24, 3.24) compared to those not taking opioids.[79] Miller *et al.* found a strong association with fractures among opioid users compared to NSAID users (hazard ratio = 4.9, 95% CI: 3.5-6.9) in a study of 17,000 older adults (mean age 80 years, 84% females) with state pharmaceutical plans.[80] Data in this area are limited and studies have not exclusively reported outcomes in women; however, it appears that high dose opioid prescriptions in this population may be associated with falls, an important consideration for prescribing pain management in women over the age of 60 years.

Summary

In summary, opioid use has increased substantially among women in recent years. These trends are particularly apparent in the United States where trends are influenced by physician prescribing patterns but are also occurring in Canada, where opioid use and addiction are now significant sources of morbidity and mortality. Evaluation of the health and safety of long-term use of opioids is highly relevant to clinical practice. We briefly summarize the current literature based on our review and highlight crucial gaps:

- *Fertility.* Long-term use of opioids exposes women to unique risks, and there may be implications for endocrinopathy and reduced fertility. Opioids have been associated with endocrine dysfunction, leading to amenorrhea and reduced fertility in women. However, the data are limited in this area, with small studies conducted before current increases in opioid use.
- *Pregnancy and neonatal risks.* Several large studies have demonstrated associations between maternal use of opioids in pregnancy with adverse outcomes including preterm birth, small for gestational age, and congenital anomalies. However, study populations are heterogeneous with illicit opioids and OAMT with variably study quality. Associated newborn complications, such as withdrawal in newborns, have also increased, and require in-patient monitoring for NAS. Non-pharmacologic treatments, such as rooming-in, skin-to-skin bonding, quiet environment and low-lighting, may be beneficial alone or with management with morphine and clonidine. Data also suggest that there may be longer term implications for children's mental health and developmental progress although this evidence is limited and inconclusive.
- *Breastfeeding.* Pharmacokinetic data suggest that opioid medications can concentrate in breastmilk, although the concentrations appear to be below clinical thresholds that may pose risks in newborns. There may be important advantages of breastfeeding/skin-to-skin bonding in this population,

including alleviation of symptoms related to NAS; challenges to establishing breastfeeding in this population should be acknowledged and supports made be available.

- *Older age.* Use of prescription opioids may be common in older age, and while studies in this area were not generally stratified by sex, several reported on populations which were majority female. Risks for older women may include increased risk of fracture especially with higher-dose opioid medication.

Risks and potential harms associated with opioid use vary across the life course. Studies show that women appear to have more persistent pain compared to men, and may be prescribed opioids more frequently, and at higher doses. Opioid use is associated with risks in pregnancy and the perinatal period and may be related to risks in childhood. Understanding the potential developmental effects on children is critical. More research is needed on the potential effects of long-term opioid use among younger women, on fertility and in women without substance misuse issues. Additional research is needed to provide decision makers with guidance for initiatives aimed at stemming the tide of the opioid epidemic and shaping updated comprehensive public health messaging for women in pregnancy and across the life course.

306   **Acknowledgements**

307   This work was partially supported by the Public Health Agency of Canada. The funding source
308   had no involvement in the study design; in the collection, analysis and interpretation of data; in
309   the writing of the report; and the decision to submit the article for publication.

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