

Reviewing the Evidence on Prenatal Opioid Exposure to Inform Child Development Policy and Practice

Andi Camden, Madeleine Harris, Sophia den Otter-Moore, Douglas M. Campbell and Astrid Guttman

Abstract

Prenatal opioid use is increasingly common and can have adverse impacts on maternal and child health. In Ontario, there are no clear guidelines or universal programs to support the healthy development of children with prenatal opioid exposure. We present the epidemiology of prenatal opioid exposure in Ontario, summarize research examining child health outcomes with a focus on child development, review emerging guidelines for child health and developmental surveillance and highlight promising programs. We emphasize the need to strengthen current Canadian recommendations for routine enhanced developmental and vision screening and ensure funding for evidence-based integrated maternal/child services.

The Issue

The ongoing opioid crisis, which has worsened during the COVID-19 pandemic, affects pregnant women and their children and necessitates a public health and healthcare system response. Opioid use in pregnancy – including therapeutic use for pain management, treatment of opioid use disorder (OUD) and non-medical use of illegally obtained opioids – has increased dramatically over the past two decades in North America (Brogly et al. 2017; Haight et al. 2018). Approximately 1 in 20 (5.3%) infants born in Ontario have prenatal opioid exposure (POE), with higher rates in those whose mothers are younger and from low-income neighbourhoods or rural areas (Camden et al. 2021). High rates (30%) have been documented in First Nations communities in Northwest Ontario (Dooley et al. 2018). POE is associated with adverse health and developmental outcomes in children, and the impact is often compounded by complex and interrelated social, environmental and clinical factors (Lee et al. 2020; Yazdy et al. 2015). Currently, there are no clear clinical standards in place to

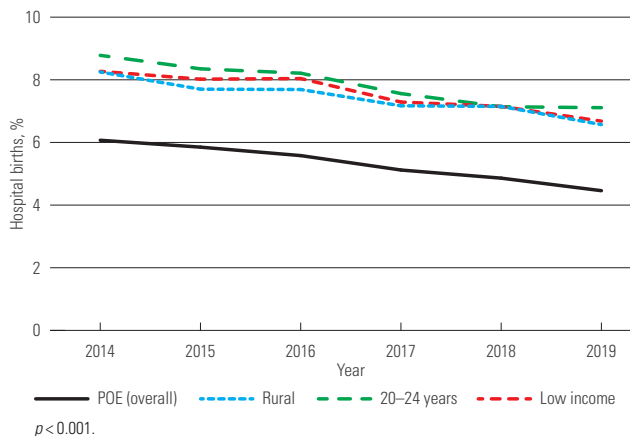
support healthy development of children with POE beyond the neonatal period, and much of the research on child outcomes is very recent. We present a review of some of our population-based research on the epidemiology of POE in Ontario, the social and medical contexts underlying maternal opioid use and dependence and the current literature on the impact of POE on child health outcomes, especially development. We review current guidelines focused on child health surveillance as well as promising programs for mother–infant dyads that include emphasis on child development. Finally, we reflect on the need for strengthening Canadian recommendations and provincial approaches to developmental and health surveillance for children with POE.

Trends in Prenatal Opioid Exposure and Neonatal Abstinence Syndrome

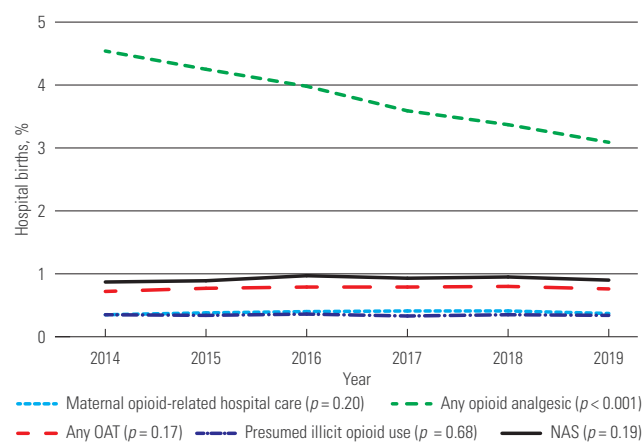
After two decades of steady increases, POE has decreased from 6.1% in 2014 to 4.5% in 2019 in Ontario, representing approximately 5,100 births in 2019 (Figure 1) (Camden et al. 2021). Declining rates were largely due to decreases in the use of opioids for pain, while rates of opioid agonist therapy (OAT) for treatment of OUD and opioid-related harm during pregnancy remained stable during this period (Camden et al. 2021). The Sioux Lookout Meno Ya Win Health Centre provides a specialized integrated pregnancy program including opioid addiction treatment for a number of First Nations communities in northwestern Ontario. In the centre’s catchment area, rates of POE documented between 2009 and 2015 have been stable since 2012, and the majority (76.9%) of POE is now a result of OAT (Dooley et al. 2018). However, rates of POE may have increased during the COVID-19 pandemic as health disparities and barriers to care for people with substance use disorders have exacerbated (Jones et al. 2021).

FIGURE 1.
Temporal trends in prenatal opioid exposure among all hospital births in Ontario, 2014–2019

a. Prevalence of prenatal opioid exposure, overall, and by select maternal characteristics



b. Type of opioid exposure during pregnancy*[§]



NAS = neonatal abstinence syndrome; OAT = opioid agonist therapy; POE = prenatal opioid exposure.

* Type of opioid exposure is not mutually exclusive.

§ NAS is based on live hospital births.

Source: Adapted from Camden et al. 2021

A short-term implication of POE is neonatal withdrawal, referred to as neonatal abstinence syndrome (NAS) or neonatal opioid withdrawal syndrome. NAS requires observation and often treatment for infant withdrawal symptoms after birth, although non-pharmacologic interventions (e.g., skin-to-skin care, swaddling) and the ability of infants to room in with their mothers are effective either alone or in conjunction with medication (Lacaze-Masmonteil and O’Flaherty 2018). NAS occurs in 55% to 94% of infants with significant POE, varying by type, timing and frequency of opioid exposure and polysubstance use (Hudak et al. 2012). In Ontario, the incidence of NAS increased five-fold between 2003 and 2014, with 6 of every 1,000 live births diagnosed with NAS in 2014, and was

accompanied by an increase in NAS-related total hospital costs from \$8.3 million in 2010 to \$12.6 million in 2014 (Filteau et al. 2018). Our more recent analysis found relatively stable rates of NAS from 6.8 to 6.9 per 1,000 live births between 2014 and 2019 in Ontario.

Prenatal Opioid Exposure and Maternal Health

The impact of POE on children’s health and development is inextricably linked with the health and well-being of their mothers. We have documented the large range of maternal socio-demographic, environmental and clinical characteristics related to the type of prenatal opioid use in Ontario. For example, compared to women using opioids for pain, women on OAT and those using illegally obtained opioids have higher rates of social risk factors related to the root causes and consequences of their opioid dependence (e.g., living in poverty, a history of being assaulted, criminal justice system involvement and the experience of having infants apprehended by social services). Many have a history of severe mental illness and non-opioid substance use. Women using opioids for pain are less likely to have the same degree of socio-economic disadvantages than those on OAT, but are still at a higher risk than the general population (Camden et al. 2021). Using data from both Ontario and England, UK, we have shown that 1 in 20 mothers of infants with NAS die within 10 years of delivery, which represents greater than a 10-fold increased risk compared with other mothers (Guttmann et al. 2019). Many of these socio-demographic and mental health characteristics of mothers who use opioids in pregnancy drive mother–child separation at birth through infant apprehension by social services. In Ontario, infant discharge to social services at birth ranges from 1% among women with prenatal opioid analgesic use to 17% among women using illegally obtained opioids in pregnancy (Camden et al. 2021). Understanding the different contexts of opioid use has important implications for strategies to address both maternal well-being and child health and development.

Perinatal and Infant Health Outcomes

Previous research has shown that compared with unexposed infants, infants with POE and NAS have an increased risk of low birth weight (Lisonkova et al. 2019; Nørgaard et al. 2015), preterm birth (birth before 37 weeks) (Alemu et al. 2020; Brogly et al. 2021; Corsi et al. 2020; Maeda et al. 2014) and stillbirth (Alemu et al. 2020; Maeda et al. 2014); and have poor fetal growth (Alemu et al. 2020; Maeda et al. 2014). The teratogenic effects of POE are still not well understood. Although some studies have shown that POE can increase the risk of congenital abnormalities, a systematic review concluded that, overall, the evidence of this relationship is of varied quality and findings are mixed (Lind et al. 2017).

The elevated risk of adverse perinatal outcomes with POE and NAS can result in more frequent and intensive hospitalizations. Compared with unexposed infants, those with POE are hospitalized for longer durations at birth and are more likely to need neonatal intensive care (Corsi et al. 2020; Witt et al. 2017), largely related to the need for observation and treatment of their withdrawal. However, they also have increased rates of readmission in the first five years of life (Witt et al. 2017). POE and NAS are also associated with a greater risk of infant mortality. Studies have reported that 1% to 2% of infants with POE will die within the first year of life – a mortality rate that is 2.0 to 3.6 times greater than that of unexposed infants (Brogly et al. 2017; Leyenaar et al. 2021; Uebel et al. 2020; Witt et al. 2017), with some of this increased risk of mortality partially attributed to infant health characteristics such as prematurity (Brogly et al. 2017; Leyenaar et al. 2021; Uebel et al. 2020; Witt et al. 2017). In these studies, the most frequently reported causes of death were sudden infant death syndrome (SIDS) and other “ill-defined” causes and injuries (Brogly et al. 2017; Leyenaar et al. 2021; Uebel et al. 2020).

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Developmental Health

An increasing number of studies suggest that POE, as a result of both illegally obtained and prescribed opioids, is associated with long-term adverse developmental outcomes. Results from four recent meta-analyses, summarizing over 50 studies, consistently demonstrate worse outcomes for children with POE (Andersen et al. 2020; Lee et al. 2020; Rees et al. 2020; Yeoh et al. 2019). Developmental domains affected include cognition, language, motor function, socio-emotional skills and visual deficiencies such as strabismus and nystagmus. For example, meta-analytic evidence examining the impact of POE (due to OAT or illegally obtained opioids) on cognitive outcomes concluded that children exposed to opioids prenatally are three times more likely to have a severe intellectual disability (Andersen et al. 2020; Lee et al. 2020; Rees et al. 2020; Yeoh et al. 2019). However, many studies had important limitations (e.g., small sample sizes, observational designs) and differences in study characteristics (e.g., type of opioid exposure, age of assessment), making it difficult to draw definitive conclusions about the direct effect of opioid exposure. As reviewed, maternal opioid use tends to occur in the context of socio-environmental deprivation, mental health challenges and polysubstance use, all of which can compromise caregiving (Azuine et al. 2019; Jaekel et al. 2021). In addition, many children with POE will be in foster care, at least temporarily, which is also a risk factor

for poor developmental outcomes. Recent population-based studies have reported higher rates of diagnoses of emotional and behavioural disorders (odds ratio 2.13–2.55) (Azuine et al. 2019) and learning disabilities (odds ratio 1.26–1.27) (Fill et al. 2018) among children with POE compared with unexposed children, even after controlling for environmental risk. While experimental animal studies have demonstrated direct links between POE and impaired neurodevelopmental and behavioural outcomes (Andersen et al. 2020), other studies report that the effects on developmental outcomes were either partly (Kim et al. 2021) or fully explained (Levine and Woodward 2018) by psychosocial factors. These mixed results suggest that developmental impairments, in this population are likely a result of a combination of biological and environmental factors in the pre- and postnatal environment. Importantly, these outcomes occurred in children with POE both with and without a diagnosis of NAS (Arter et al. 2021; Hall et al. 2019).

Studies investigating long-term outcomes following prenatal exposure to specific types of opioids found that both illegally obtained and prescribed opioid exposure during pregnancy may result in poor developmental outcomes. Meta-analytic evidence demonstrates significant effects of prenatal exposure to OAT (i.e., methadone and/or buprenorphine) on various domains of developmental functioning, including visual and psychomotor outcomes compared to unexposed controls (Andersen et al. 2020), as well as no statistically significant differences in infant cognitive development when comparing groups exposed to heroin versus OAT (Lee et al. 2020). Recent population-based studies found that effects of prenatal exposure to analgesic opioids on language competence and communication skills (Skovlund et al. 2017) and risk of neurodevelopmental disorders (Wen et al. 2021) were not statistically significant after controlling for other factors. However, in one study, differences between exposed and unexposed groups were observed in children with longer exposure and higher doses of analgesics (Wen et al. 2021).

In sum, the degree of neurodevelopmental impairment in children with POE is a result of a range of factors, including environmental variables, exposure to other substances and type of opioid. While the degree to which the opioid exposure alone plays a part in development is not fully understood, this growing body of evidence suggests that affected children are at increased risk for developmental difficulties across a range of domains.

Current Recommendations on Developmental Assessment of Children with POE

We searched for clinical practice guidelines in four countries with a high prevalence of POE (Canada, USA, Great Britain and Australia). We found that three professional societies have made recommendations regarding developmental assessment of infants and children prenatally exposed to opioids (Lacaze-Masmonteil

and O’Flaherty 2018; Patrick et al. 2020; Queensland Health 2021). The Canadian Paediatric Society recommends that discharge planning should include infant neurodevelopmental assessment by a primary healthcare provider, with consideration of community referrals such as infant development programs (Lacaze-Masmonteil and O’Flaherty 2018). The American Academy of Pediatrics (AAP) and Queensland Health made similar but stronger recommendations, highlighting the importance of developmental surveillance and early referral by the primary care provider (Patrick et al. 2020; Queensland Health 2016), with follow-up suggested for at least 12 to 24 months (Queensland Health 2016). Queensland Health also made specific recommendations for ophthalmological assessment for myopia and strabismus (Queensland Health 2016). The AAP also worked with members of the Indian Health Service within the US Department of Health and Human Services and made strong recommendations, including for developmental screening (not just surveillance) routinely conducted during well-baby visits at 9, 18, 24 and 30 months (American Academy of Pediatrics 2019). To our knowledge, there is no standardized approach or specific provincial or federal (in the case of First Nations and Inuit healthcare) implementation related to developmental screening or health surveillance for infants with POE in any Canadian jurisdiction.

Role of Integrated Programs in Supporting Mother–Infant Dyads

While a fulsome review of the evidence for multidisciplinary care of mothers with OUD is outside the scope of this article, existing clinical practice guidelines acknowledge the importance of integrated treatment models (The American College of Obstetricians and Gynecologists 2017; Ordean et al. 2017). Integrated treatment models conducted in centralized settings provide a range of medical and social services, such as addictions counselling and developmental assessment (Niccols et al. 2012). In this article, we focus on programs that also emphasize child development. Trauma-informed care is critical for the appropriate care of the mother, but it also relates to parenting support. For example, *Breaking the Cycle* (<https://www.mothercraft.ca/index.php?q=ei-btc>) is an integrated program for women who are pregnant or parenting children under six years of age in Toronto, ON, and are affected by substance use. Evaluations of *Breaking the Cycle* and other integrated programs demonstrate improved child development and emotional and behavioral functioning (Mutz et al. 2006; Niccols et al. 2012) and reduced child apprehension and parental substance misuse (Mutz et al. 2006; Poole 2000). Parents and children may also benefit from specific parenting programs shown to be effective in improving parenting capacity and decreasing child behavioural problems in families affected by opioid use (Egan et al. 2020; Gannon et al. 2017; Peisch et al. 2018).

Conclusion

Prenatal opioid use is common in Ontario and other Canadian provinces. The recent literature is clear that children with POE are at risk for a range of health and developmental concerns related both to circumstances associated with maternal opioid use and dependence and likely some direct effect of opioids, although this varies with type and amount. Although there has been a focus on infants with NAS, programs should target all infants with significant POE. While recent guidelines have highlighted the need for enhanced developmental and health surveillance, the Canadian guidance could be strengthened to include specific recommendations around more intensive developmental surveillance and the need for eye exams. Provincial and federal healthcare programs need to implement these recommendations; particular strategies for ensuring continuity of primary care and longitudinal developmental surveillance for children in foster care will be important. The higher rates of SIDS should also inform specific counselling at the time of discharge from hospital and at every well-baby visit and during home visits for those receiving services from public health nurses. For particularly high-risk infants, specialized neonatal follow-up by developmental pediatric teams – such as is the case for infants born after a short gestation period and cared for in neonatal intensive care units – could be another model of care that builds on an existing delivery infrastructure (Provincial Council for Maternal and Child Health 2015). For many mother–infant dyads, integrated programs are critical for the long-term well-being of the mother and healthy child development, but additional funding will be necessary to scale up these effective programs to meet the increased demand brought on by the opioid epidemic.

Key Takeaways Related to POE and Child Health and Development

Here we have summarized six key takeaways related to prenatal opioid exposure and child health and development:

1. Prenatal opioid exposure is common in Ontario and the rest of Canada.
2. Infants with POE are more likely to be born prematurely with low birth weight and are at a higher risk of SIDS and death due to injuries.
3. There is clear evidence of a range of developmental challenges in children with POE, including cognitive, motor and behavioural impairments, as well as visual outcomes (e.g., strabismus).
4. All children with POE should undergo enhanced developmental surveillance, including visual and neurodevelopmental assessment.

5. For children in foster care, there is a high risk of discontinuous primary care and loss to follow-up, necessitating specific strategies to ensure continuity of care.
6. Strategies that support families impacted by opioid use, including integrated treatment models and parenting programs, have the potential to mitigate the long-term developmental consequences of POE.

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About the Authors

Andi Camden, MPH, is an epidemiologist and PhD candidate in the Epidemiology Division of the Dalla Lana School of Public Health at the University of Toronto and a research trainee at The Hospital for Sick Children in Toronto, ON.

Madeleine Harris, MSc, is a medical student at the Temerty Faculty of Medicine at the University of Toronto and a research student at the SickKids Research Institute in Toronto, ON.

Sophia den Otter-Moore, MSc, is a medical student at Queen's School of Medicine in Kingston, ON.

Douglas M. Campbell, MD, FRCPC, is medical director of the NICU at St. Michael's Hospital, an associate scientist at the Li Ka Shing Knowledge Institute, Unity Health Toronto, and an associate professor of Pediatrics in the Faculty of Medicine at the University of Toronto in Toronto, ON.

Astrid Guttmann, MDCM, MSc, is a senior scientist and chief science officer at ICES, a pediatrician and clinician scientist at The Hospital for Sick Children and professor of Paediatrics, Health Policy and Public Health at the Dalla Lana School of Public Health at the University of Toronto in Toronto, ON. Astrid can be contacted by e-mail at astrid.guttmann@ices.on.ca.