

Annual Research Review: Prenatal opioid exposure – a two-generation approach to conceptualizing neurodevelopmental outcomes

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Opioid use during pregnancy impacts the health and well-being of two generations: the pregnant person and the child. The factors that increase risk for opioid use in the adult, as well as those that perpetuate risk for the caregiver and child, oftentimes replicate across generations and may be more likely to affect child neurodevelopment than the opioid exposure itself. In this article, we review the prenatal opioid exposure literature with the perspective that this is not a singular event but an intergenerational cascade of events. We highlight several mechanisms of transmission across generations: biological factors, including genetics and epigenetics and the gut–brain axis; parent–child mechanisms, such as prepregnancy experience of child maltreatment, quality of parenting, infant behaviors, neonatal opioid withdrawal diagnosis, and broader environmental contributors including poverty, violence exposure, stigma, and Child Protective Services involvement. We conclude by describing ways in which intergenerational transmission can be disrupted by early intervention. **Keywords:** Addiction; neurodevelopment; prenatal; substance use.

Introduction

Globally, an estimated 40 million people are dependent on opioids (Degenhardt et al., 2019), and close to 27 million are living with opioid use disorder (OUD; Strang et al., 2020). However, there is high variability in opioid dependence based on country. The United States leads this epidemic with around 1,347 out of every 100,000 people opioid dependent (Degenhardt et al., 2019). Over the past two decades, women of reproductive age have reported increasing opioid use (Terplan, 2017). An often overlooked “side effect” of the opioid epidemic is the effects on the developing fetus. Approximately 14%–22% of pregnant women fill a prescription for opioids, and close to 7% of pregnant women reported opioid use (Ko et al., 2020). Increases in maternal opioid use have been accompanied by a parallel increase in the drug withdrawal of opioid-exposed infants, known as neonatal abstinence syndrome (NAS), or more recently, neonatal opioid withdrawal syndrome (NOWS; Jilani et al., 2021). Despite knowledge that opioid use in the pregnant woman can impact the health of two generations – the mother and her child – there has been little focus on neurodevelopmental consequences of intergenerational transmission. The overarching goal of this article is to describe how prenatal opioid exposure affects the developing child, recognizing that this is not a singular event but an intergenerational cascade of events. We also acknowledge at the outset that this is a rapidly changing field but, even so, there are some

fundamental long-term “truths” related to prenatal opioid exposure.

Opioid use disorder

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), defines drug addiction as, “a chronic, relapsing disorder characterized by compulsive drug seeking and use despite adverse consequences.” Individuals addicted to substances show difficulties limiting their drug intake and exhibit negative emotions, such as anhedonia or irritability, when the drug is not available (Koob & Volkow, 2016). Perspectives on addiction are largely based on animal studies. Generally, opioid use triggers μ -, κ -, and δ -receptors concentrated in the central nervous system and gastrointestinal tract (Hudak & Tan, 2012). These receptors increase the firing of dopaminergic neurons in the ventral tegmental area of the midbrain, which release dopamine into the nucleus accumbens (Brown & Capili, 2020; Fields & Margolis, 2015). Dopamine is the major neurotransmitter in the brain’s reward pathway, which accounts for the rewarding effects of opioid use.

Addiction to opioids involves a three-stage cycle with distinct neurobiological underpinnings (Koob & Volkow, 2016). In the first stage (binge/intoxication), consumption of opioids results in a fast and steep release of dopamine, causing the “high” that reinforces opioid use. Activation of the dopamine system triggered by drug consumption can also activate basal ganglia, leading to conditioned reinforcement of drug-paired cues as well as enhanced incentive

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salience, and eventually to cue-induced and compulsive, habit-like drug seeking. In the second stage (withdrawal), the drug is no longer being consumed and negative affect (e.g., anhedonia, irritability) increases. This emotional dysregulation is mediated by several neurobiological circuits, including the stress response systems [e.g., hypothalamic–pituitary–adrenal (HPA) axis] and the amygdala. The third phase of the addiction cycle (craving and preoccupation with drug seeking) can manifest as executive functioning challenges such as impulsivity and compulsivity that drive drug-seeking behaviors and lead to relapse. These executive functioning difficulties are largely mediated by the prefrontal cortex. Repeated opioid use is theorized to intensify these stages and result in opioid addiction (Koob & Volkow, 2016).

Risk for addiction is a concern for any adult who is prescribed opioids. Many adults take prescription opioids as recommended by their physicians. However, opioid use can lead to opioid abuse if an individual uses the opioid in a different way than prescribed, including taking a larger dose, changing the route of administration (e.g., crushing and snorting), or using someone else's prescription (Meltzer et al., 2011). Opioid abuse can lead to opioid dependence when the individual experiences a physiological response to withdrawal of the opioid, or develops a tolerance for the drug and requires more of the opioid to reduce these physiological effects of withdrawal (Ballantyne et al., 2012). The DSM-5 combines the concepts of opioid abuse and opioid dependence into “Opioid Use Disorder,” which, given the highly addictive properties of opioids, is considered a chronic and relapsing disorder. It is important to note that while dependence corresponds with physiological adaptation leading to tolerance and withdrawal, addiction is considered a psychological phenomenon due to the pathological pursuit of feelings of reward and/or relief through drug use. This distinction is vital because opioid-exposed newborns are often referred to as “addicted,” a misnomer but an example of the misguided and often harmful labeling associated with this population.

Opioid use disorder in pregnant women

Historically, pregnant women were prescribed morphine and heroin for morning sickness. Prior to 1914, morphine and heroin were legal and could be bought over-the-counter, thus increasing mothers' likelihood for addiction. The Harrison Narcotic Act was passed in 1914, which attempted to regulate the production, importation, and distribution of opioids (Berridge, 2009). However, illicit heroin use continued. In the 1970s, methadone—a synthetic opioid medication with longer lasting effects—was used to help treat adults addicted to heroin (Berridge, 2009), followed by buprenorphine in 2002 (Sporer, 2004).

The most recent opioid epidemic was initiated in the 1990s and early 2000s when prescriptions for opioids surged (Donroe et al., 2018). In 1996, the American Pain Society declared pain as the “5th vital sign,” which may have contributed to the rise in prescription opioid use and the current opioid epidemic. There are clear regional variation and demographic differences in opioid use, with the highest use often reported in the northeast, mountain west, and in certain states in the southeast such as West Virginia and Kentucky (Guy et al., 2017). Prescription opioid use was typically highest among non-Hispanic whites and American Indian and Alaskan Natives, though recent reports suggest that opioid use is increasing in non-Hispanic Black adults (Harrison et al., 2018).

Risk factors for opioid use disorder and implications for neurodevelopmental consequences of intergenerational transmission

Beyond regional and demographic differences in opioid use and misuse, there are factors specific to pregnant women that increase risk for OUD and may predispose children in the next generation to adverse health and developmental sequelae. The mechanisms implicated in this risk transmission are complex, operate at multiple levels of analysis, and involve transactional interactions across time. Figure 1 shows biological and environmental risk factors prior to, during, and after pregnancy that are associated with OUD, how these co-occurring risks may be transmitted intergenerationally, affect newborn neurobehavior, contribute to the quality of caregiver–infant interactions (center of figure), and affect neurodevelopmental outcomes.

Prepregnancy factors

Risk factors prior to pregnancy can impact pregnancy, birth, and child outcomes in the context of OUD. Exposures to adverse childhood experiences (ACES; e.g., abuse, neglect; Felitti et al., 1998; Leza et al., 2021) and poverty disproportionately affect pregnant women with OUD. Fifty to 80% of women with substance use disorders report experiencing child maltreatment. The highest rates of substance use in adult women are observed among those who have experienced ACES (Cunradi et al., 2020). Exposure to ACES and stressors such as poverty (Ghertner & Groves, 2018) tend to be replicated across generations and likely alter the developing fetal central nervous system even when the exposure occurred before the pregnancy (Scorza et al., 2019). For example, greater numbers of maternal ACES made an independent contribution (above prenatal-specific stress) to infant respiratory sinus arrhythmia, indicating potential disruptions in infants' parasympathetic nervous system responding (Gray

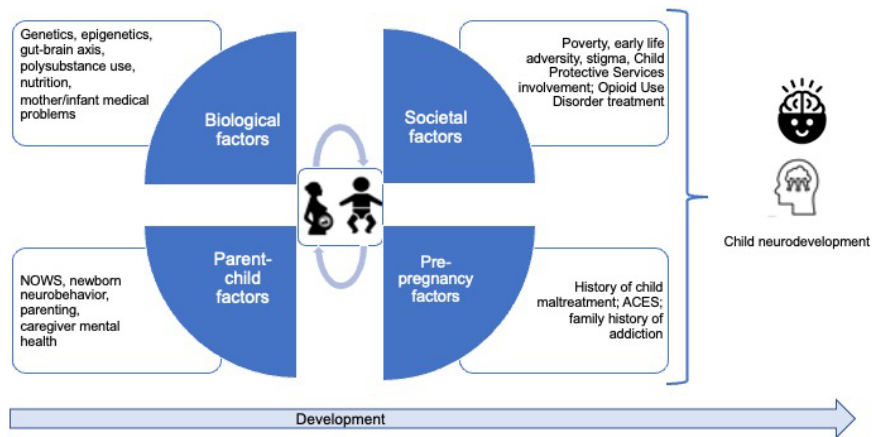


Figure 1 A conceptual model depicting a two-generation approach for understanding neurodevelopmental outcomes among children with prenatal opioid and other substance exposures

et al., 2017). In recognition that pregnant women at risk for OUDs may have experienced significant trauma in their early childhoods, studies such as the Healthy Brain and Child Development Study are integrating knowledge about early life stress and trauma into protocols on the long-term neurodevelopmental consequences of prenatal opioid exposure (Jordan et al., 2020).

Exposure to ACES can exacerbate symptoms of addiction and increase risk for child maltreatment. In mothers using substances, violence exposure and current trauma symptoms predicted lower parenting competence (Brown et al., 2021). Substance use in women also increases the risk for child maltreatment (Dubowitz et al., 2011), and this risk was stronger if women were experiencing additional risk factors such as poverty (Ondersma, 2002), increasing the likelihood that children are placed in foster care (Moreland et al., 2021). Children in foster care whose biological parent is experiencing a substance use disorder have poorer reunification and attachment outcomes and experience more time in foster care compared to children in foster care whose parents do not have a substance use disorder (Mirick & Steenrod, 2016). In a study of 1,092 children with prenatal cocaine and/or opioid exposure, each caretaker change was associated with a decrease in adaptive behavior and an increase in problem behavior (Bada et al., 2008). Instability in living arrangements was a stronger predictor of these outcomes compared to prenatal exposure to substances such as alcohol, tobacco, marijuana, cocaine, and opioids (Bada et al., 2008). This finding has important implications for policies related to child removal from the biological family. For example, 16 states have mandatory reporting laws, which may increase the likelihood that the child experiences a higher number of caretaker changes, disrupting the developing infant/parent relationship with potential negative downstream effects on child behavior and mood including psychopathology (Kozhimannil et al., 2019).

Risk factors for opioid use, such as exposure to poverty, frequently replicate across generations and could, in combination with prenatal opioid exposure, increase risk for neurodevelopmental challenges. In fact, these postnatal exposures may have stronger effects on child development than the opioid exposure itself. In a sample of over 900 adolescents with prenatal substance exposure, low parental involvement and violence exposure were stronger predictors of risk-taking behavior than prenatal exposure to cocaine, opioids, tobacco, alcohol, and marijuana (Lambert et al., 2013). Despite the risk of early adversity, certain features of the home environment could be protective. In children with prenatal exposure to methamphetamine, primary caregivers who were able to support their preschooler's developmental and emotional needs had children with fewer internalizing and externalizing problems at age 5 (Twomey et al., 2013).

Maternal genetics are another factor that may increase risk for OUD and operate as an intergenerational mechanism conferring risk for poor outcomes in children. Like other substance use disorders, OUD has high heritability, with approximately 50% of risk attributable to genetic factors (Goldman et al., 2005; Kendler et al., 2000). Certain polymorphisms in dopamine receptors *DRD3* and *DRD4* are more prevalent in adults with opioid addiction and dependence and are also associated with increased sensation seeking and novelty seeking, traits which may contribute to opioid dependence (Mistry et al., 2014). Polymorphisms in *OPRM1*, which encodes the μ -opioid receptor, may be responsible for differential expression and sensitivity of μ -opioid receptors in the brain as well as vulnerability to opioid addiction (Levrán et al., 2012; Yiannakopoulou, 2015). Genetically-based differences in opioid metabolism (Nielsen et al., 2015; Yiannakopoulou, 2015) may also contribute to risk for addiction: poor opioid metabolizers may be at increased risk of overdose, whereas rapid metabolizers may be at increased risk of excessive opioid intake.

Polymorphisms of the mu (*OPRM1*) and kappa (*OPRK1*) opioid receptor gene not only influence risk for OUD but are also linked to severity of NOWS (Wachman et al., 2013, 2015). Interestingly, genotypes of *OPRM1* that are associated with reduced opioid receptor binding are related to higher risk for opioid addiction in adults but may be protective against severe withdrawal in neonates (Wachman et al., 2013). Dopamine receptor genes (e.g., *DRD2*) and genes involved in the stress response system (e.g., *COMT*) have also been found to be associated with length of stay and need for pharmacological treatment with one or more medications (Wachman et al., 2013). Thus, genes transmitted from mother to child may be responsible for short-term outcomes such as NOWS severity as well as long-term risk for opioid addiction and other externalizing disorders.

The risk factors and mechanisms described thus far (ACES, poverty, and genetics) may also operate in tandem. For example, links between certain genotypes (e.g., polymorphisms of *DRD4*) and adverse child outcomes may be exacerbated in the context of environmental adversity (e.g., maternal insensitivity, interparental conflict; Bakermans-Kranenburg & van Ijzendoorn, 2006; Davies et al., 2019; Windhorst et al., 2015). These findings show how genetic and environmental correlates of maternal OUD may work together in the intergenerational transmission of substance use disorders and other behavioral outcomes.

Pregnancy factors

Use of substances beyond opioids present risk associated with OUD during pregnancy, so much so that prenatal opioid exposure effects on the newborn may be better characterized as polysubstance exposure effects (Jarlenski et al., 2020). For example, pregnant women with a diagnosis of OUD were also likely to have a diagnosis of amphetamine use and tobacco use disorder, compared to alcohol, cannabis, cocaine, or other sedative disorder (Jarlenski et al., 2020).

Comorbid mood disorders are also commonly experienced among pregnant women with OUD. Approximately 36%–38% of pregnant women using opioids also experience mood disorders such as major depressive disorder, and approximately 20% of pregnant women who use opioids have a prescription for psychotropic medication (Shen et al., 2020; Venkatesh et al., 2020). Furthermore, mothers who use opioids while pregnant are more likely to have high levels of emotion dysregulation, inadequate nutrition, poor prenatal care, and medical comorbidities such as hepatitis (Conradt et al., 2018). When examining how prenatal opioid use can impact neurodevelopmental outcome, it is essential to consider effects of these wide-ranging comorbidities.

Societal influences may also impact the health of the pregnant woman and her child. Despite

knowledge rooted in neuroscience that drug addiction is a disease, substance use in pregnancy is thought to be a matter of choice, and women are blamed for not having enough self-control to stop using substances (Schiff et al., 2022). Pregnant women report experiencing harsh judgment by hospital staff (e.g., being called a “drug addicts” or “dope fiend”), being rejected from OB/GYN clinics because they are on medication treatment for OUD, and facing criminalization of their pregnancy (Syvertsen et al., 2021), including child removal. These experiences threaten the likelihood that pregnant women receive treatment for OUD and seek prenatal care altogether, especially for women of low socioeconomic status and women of color (Stone, 2015). Since treatment programs are associated with healthier pregnancies and better fetal outcomes, reducing the stigma around prenatal substance use is a vital step in combating this disease and its consequences on the child (Wolfson et al., 2021).

Postnatal factors

The three months following childbirth – sometimes called the “4th trimester” – is a vulnerable period for women with OUD and their infants. Risk for overdose is a concern, given that maternal mortality increases by more than 200% when opioids are involved (Gemmill et al., 2019). Poor access to medications for OUD after birth may be a contributing factor, which may disproportionately impact Black and Hispanic women (Schiff et al., 2021). Women in treatment for OUD also report that parenting a newborn with NOWS, struggling with depression and anxiety, and experiencing stigma all contribute to a challenging recovery process (Martin et al., 2022).

Many mothers with OUD are concerned about how their opioid use has impacted the child and ask for ways in which they can best support their child’s development (Syvertsen et al., 2021). However, because of mental health comorbidities, a history of trauma, a stigmatizing healthcare environment, and poor models of parenting in their own lives, caregivers with OUD face significant parenting challenges (Kahn et al., 2017). Rutherford and Mayes (2017) developed the reward-stress dysregulation model of addiction and parenting to explain how addiction to substances can lead to decreased maternal responsiveness and sensitivity to the natural rewards most parents not struggling with addiction experience with their infant.

Infants contribute to their own environment, and factors such as newborn neurobehavior (Gao et al., 2022), temperament, and signs and symptoms associated with a NOWS diagnosis, could affect the quality of the caregiver–child interaction. Few studies assess ways in which the infant may contribute to the quality of dyadic interactions, and studies that have been published include small sample sizes. For example, prolonged hospitalization, in some cases

due to NOWS diagnosis, resulted in greater parent-reported parent-child dysfunctional interaction scores (Bakhireva et al., 2019). In this study, infants with prenatal opioid exposure had lower observed self-regulation scores during mother-infant interaction, which could undermine parenting self-efficacy (Bakhireva et al., 2019). In another study with mothers in treatment for OUD, these mothers had more difficulty sensitively responding to infant cues, and their infants were less responsive to their caregiver during a mother-infant feeding interaction, compared to an unexposed control group (Maguire et al., 2016).

Unique challenges in the parent-child relationship, the experience of mental health comorbidities in the caregiver with OUD, and broader societal stressors such as exposure to poverty and stigma make the development of successful parenting interventions for families struggling with OUD difficult. However, there are some promising interventions to improve parenting outcomes between caregivers and their infants that account for the complex comorbidities caregivers with OUD experience while targeting stress and reward neurobiological (FIND; Fisher et al., 2016) or attachment mechanisms (Attachment and Biobehavioral Catchup; Dozier & Barnard, 2017). Pregnancy is also an opportunity for early intervention and prevention efforts that are family focused and take a more holistic approach to care, given that once newborns and their caregivers are discharged from the hospital there are so few support services available during this sensitive period in the family's life. Integrated care models were developed based on this understanding that pregnant women with OUD face significant barriers to care, including numerous prenatal appointments in addition to treatment for addiction. These care models include co-located addiction and obstetric care options, which makes it easier for mothers to attend both appointments, leads to more coordinated care, and improves attendance at appointments, resulting in significant reductions in preterm births. Once the child is born, pediatric components are also included in these integrated care models, and referral to early intervention which supports child safety and increases the likelihood that parenting and child behavioral challenges are addressed early in development.

Child factors

Neonates exposed to opioids in utero display heterogeneous medical and behavioral profiles (Jilani et al., 2021). These differences contribute to the intergenerational transmission of opioid use effects and may alter the neurodevelopmental trajectories. In this section, we discuss factors that influence diagnosis and treatment of NOWS and how they may contribute to the cascade of events following maternal opioid use.

Diagnosis of NOWS

NOWS is a drug withdrawal syndrome seen in 50%–80% of children with prenatal opioid exposure (Reddy et al., 2017). It is characterized by autonomic instability, high-pitched cry, irritability, tremors, and difficulty feeding and sleeping (Jilani et al., 2021). The pathophysiology of fetal opioid exposure is more complex than in adults due to rapidly emerging neurological development (Kocherlakota, 2014). Opioids readily cross the placenta, and this transfer rate is influenced by pharmacokinetics, placental characteristics, and maternal factors (Włoch et al., 2009). Opioids, such as methadone and buprenorphine, are both lipid soluble and transfer passively through the placenta (Gordon et al., 2010). This rate of drug transfer increases as the pregnancy progresses; the placental barrier thins, increasing the surface area and improving blood flow to compensate for escalating fetal demand for oxygen, nutrients, and hormones (Syme et al., 2004). Opioids themselves can generate changes to the placenta, including cellular functions and structural vascular changes, which may additionally impact extent of opioid transfer. Further, heightened maternal metabolism reduces the half-life of opioid medications by 50% in the third trimester. Thus, the dose of medication prescribed for opioid replacement therapy is often increased as pregnancy progresses (Bogen et al., 2013).

There is also high variability in the amount of opioids that reach fetal circulation based on individual drug use (e.g., use of heroin with methadone facilitates transfer across the placenta) and placental characteristics (e.g., healthy and normative placental functioning may increase the transfer rate of opioids due to increased blood flow; there is also variability in the presence of aromatase and P-glycoprotein), as well as maternal and fetal factors (e.g., metabolism, opioid receptor development and sensitivity). All of these factors may impact the level of opioids exposure and may help explain some of the variability in neonatal opioid withdrawal (Kocherlakota, 2014).

The communication between the gut and the brain, known as the gut-brain axis, may also play a role in the pathophysiology of NOWS (Figure 2). The gut and the brain are joined by the 10th cranial or vagus nerve, which innervates the gut and plays a role in digestion. Opioid receptors are distributed throughout the digestive tract and central nervous system, suggesting that opioid exposure may exert bidirectional influences on the gut-brain axis (Rueda-Ruzafa et al., 2020). For example, opioids can cause constipation in adults by activating μ -opioid receptors in the gut and slowing digestion (Simpson et al., 2021). Gut microbes and inflammation are thought to contribute to infant cry patterns including infant colic (Sung & Pärty, 2017). NOWS symptoms include autonomic nervous system

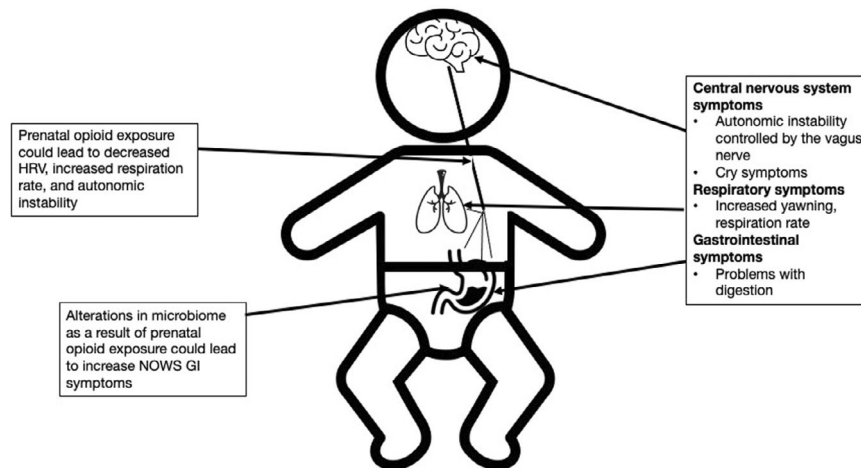


Figure 2 The gut–brain axis as a mechanism of risk for neonatal opioid withdrawal syndrome

instability and respiration, controlled in part by the vagus nerve, gastrointestinal problems such as diarrhea, and central nervous system symptoms, all of which could modulate – and be modulated by – the gut–brain axis (Figure 2).

The vagus nerve can also regulate immune responses in the gut by releasing acetylcholine which can suppress immune system functioning (Simpson et al., 2021). Inflammation originating in the gut can activate central nervous system stress response including the hypothalamic–pituitary–adrenal axis which may then release more of the stress hormone cortisol (Simpson et al., 2021). Oxytocin is present in the gut and brain of the neonate and is a powerful anti-inflammatory neuropeptide that may help protect the brain during a vaginal birth by reducing inflammatory cytokine in the brain (Kingsbury & Bilbo, 2019). However, birth interventions including elective caesarean sections and the stimulation of labor using oxytocin may interfere with exposure to oxytocin signaling in the neonate, which could have an effect on neonatal brain development (Kingsbury & Bilbo, 2019). Some pregnant women with OUD experience comorbidities, such as placental abruption, increasing their likelihood of delivering via caesarean-section (Miller et al., 2019). Thus, an understudied potential mechanism by which prenatal opioid exposure can alter neurodevelopment and NOWS risk is via the gut–brain interactions.

The role of epigenetic modification during the preant period in predicting NOWS severity is an additional mechanism of transmission of risk for children with prenatal opioid exposure. Epigenetic modifications such as DNA methylation impact the potential for gene expression. The majority of studies in this area have investigated *OPRM1*, finding that higher levels of DNA methylation in the promoter region are linked to more severe NAS (Wachman et al., 2014). The reason for this may be that higher methylation downregulates protein expression of mu-opioid receptors that in turn could increase the

need for pharmacological treatment to manage NOWS symptoms. Others have investigated DNA methylation of opioid transport (e.g., *ABCB1*) and metabolism (e.g., *CYP2D6*) genes but despite finding differences in methylation for opioid-exposed versus nonexposed neonates, they did not find associations with NOWS severity (McLaughlin et al., 2017). A limitation of existing genetic and epigenetic work thus far is that samples have tended to be small, and most studies investigate candidate genes rather than using epigenome-wide methods. There has also been some lack of replication across independent cohorts, possibly due to varying sample characteristics (e.g., geographic region, extent, and types of concurrent exposures). Existing studies also lack long-term follow-up, meaning that it is unclear how genetic and epigenetic differences at birth predict health and development outcomes beyond the neonatal period.

Absent biological markers, the diagnosis and treatment of NOWS is based on observation and clinical signs, the “gold standard” being the Neonatal Abstinence Scoring System, also known as the Finnegan Scale (Finnegan et al., 1975). The literature is replete with frustration and dissatisfaction with the Finnegan Scale including criticisms of the length of the tool (Jansson et al., 2009; Maguire et al., 2013), its inherent subjectivity (Timpson et al., 2018), its validity and reliability (Singh & Davis, 2021) and the need to disturb infants for formal assessments (Grossman et al., 2017). There are also concerns that the Finnegan Scale may overestimate the need for pharmacologic treatment by including signs that may not be clinically significant resulting in increased length of hospital stays and hospital costs (Grossman et al., 2017). If clinical judgement is the sole factor involved in NOWS treatment, staff bias and stigma could alter how these staff determine that a newborn is experiencing NOWS symptoms (Schiff et al., 2022), affecting whether or not the newborn is prescribed medication

for NOWS. There are mounting efforts to reduce the need for pharmacological treatment.

Accurate diagnosis of NOWS is critical because not all infants exposed to opioids during pregnancy develop clinically significant symptoms of NOWS. False positives can result in neonates unnecessarily receiving pharmacological treatment (usually morphine) with corresponding prolonged hospitalization, possible separation from caregivers, and substantial cost, or false negatives, including unnecessary treatment that could lead to serious medical problems. Moreover, the landscape of NOWS is changing with the increased use of nonpharmacological treatment, despite recommendations since the 1970s that nonpharmacological care be used as the first-line therapy for NOWS, which could potentially reducing pharmacological treatment (Berkwitt et al., 2018; Grossman et al., 2018).

The Eat, Sleep, Console (ESC) Care Tool (Grossman et al., 2017, 2018) was developed as an alternative to the Finnegan. ESC focuses on nonpharmacological treatment as the first-line treatment for infants with NOWS. If the infant meets criteria for sleeping, eating, and consoling, pharmacological treatment is not initiated or escalated. If the infant is having difficulties in one of these areas related to NOWS, staff and caregivers first attempt to optimize nonpharmacological interventions. If these procedures are not successful, pharmacological treatment is initiated or escalated. Like the Finnegan, the ESC tool is also administered every 3–4 hr, and ratings are still subject to staff bias. Early reports using the ESC tool are encouraging in terms of decreasing the use of pharmacological intervention and reducing length of stay; however, most reports are retrospective and little psychometric data are available. There is also no clear evidence that one approach is better than the other. However, an NIH clinical trial is underway comparing the Finnegan with ESC ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04057820) Identifier: NCT04057820).

Clinical signs of NOWS include dysfunction of the central, autonomic, respiratory, and gastrointestinal systems (e.g., tremors, excessive/high-pitched crying, breathing, and intestinal problems; Stover & Davis, 2015). Crying is a key component of both the Finnegan and ESC assessments. Recent pilot work using machine learning, acoustic analysis of cries was found to correctly identify infants with NOWS. Acoustic cry analysis reflects the pathophysiology of withdrawal with projections to the brain stem, autonomic nervous system, and gut and could serve as an objective biobehavioral/biomarker of NOWS, leading to improvements in our ability to detect early – and treat – newborns who may develop NOWS.

Treatment of NOWS

The kind of treatment the newborn receives for NOWS can have implications for intergenerational

risk transmission. NOWS treatment can be categorized as nonpharmacological and pharmacological. Nonpharmacological treatment options could have different consequences for the developing caregiver–infant relationship compared to pharmacological treatment options, though this hypothesis has never been tested. Below we describe both types of treatments, and how they may impact the amount of time the caregiver is with the child, the extent to which the caregiver is encouraged to breastfeed and soothe the child, and the degree to which the caregiver is seen as a part of the child’s care team. If caregivers are empowered to care for the infant with prenatal opioid exposure, they may feel more self-efficacy once discharged from the hospital, which could be protective or provide a buffer against any challenges the family experiences in the first years of life (Garnett et al., 2020; Hostinar et al., 2014; Tronick, 2017).

Treatment for NOWS varies widely across hospitals, and few randomized controlled trials have been conducted to evaluate existing treatment guidelines (Piccotti et al., 2019). Nonpharmacological treatments may be the earliest, and most potent intervention to support the caregiver–infant relationship, helping to disrupt the intergenerational transmission of stress by reinforcing the attachment relationship. Nonpharmacological treatments are designed to promote caregiver involvement in treatment and care of the newborn with prenatal opioid exposure. Nonpharmacological treatments have been implemented since the 1970s, in many hospitals as the first treatment option provided to the infant (Velez et al., 2021). These treatments typically involve “rooming in,” or keeping the newborn in the same room as the caregiver so that the caregiver can breastfeed the newborn more easily, and respond to cues for comfort and care. Because the newborn with prenatal opioid exposure may be more sensitive, sounds are kept to a minimum and lights are kept dim. Swaddling and clustered care are also recommended to protect infant sleep. In some hospitals, volunteers help to rock and hold the baby if the caregiver is unavailable (Piccotti et al., 2019).

Rooming-in can impact both generations by reducing NOWS symptoms in the infant and reducing the likelihood that mother and infant are separated after the mother is discharged from the hospital, thereby supporting the caregiver–infant attachment relationship. Skin-to-skin contact with the caregiver or other support person such as a partner or grandparent is encouraged. Nursing support is provided, and the caregiver and infant are almost continuously together, which allows the caregiver to learn the infant’s cues and bond with the infant and could reduce infant fussiness or irritability.

Pharmacological interventions are typically initiated when the frequency and intensity of NOWS symptoms increase. First-line treatments typically include an opioid, such as morphine or methadone. If NOWS symptoms remain elevated, adjuvant

therapy may be necessary, which typically includes clonidine or phenobarbital. The substance that a pregnant woman uses to treat OUD, such as buprenorphine, is being evaluated in recent trials to determine the efficacy of neonatal administration of buprenorphine as a treatment for NOWS.

NOWS diagnosis, and presumably treatment, can reduce the likelihood of neonatal death (Leyenaar et al., 2021). A medical record review of over 1 million maternal–infant dyads showed that the odds of death in the first year of life for newborns with prenatal opioid exposure who were not diagnosed with NOWS were 72% greater compared to newborns without prenatal opioid exposure. The reasons for this discrepancy are unclear but may include, as Leyenaar speculate, insufficient follow-up of newborns with prenatal opioid exposure who were not given a NOWS diagnosis. It could also be that a NOWS diagnosis was protective, and that greater attention was paid to these newborns before and after treatment (Leyenaar et al., 2021).

Maternal psychiatric comorbidities and NOWS

The role of psychiatric comorbidities experienced by the mother affecting NOWS is just beginning to be understood and again highlights how even after the child is born, prenatal exposures can alter the clinical care of the newborn with prenatal opioid exposure (Benningfield et al., 2010; Faherty et al., 2018; Wachman et al., 2011). Pregnant women who use opioids and have depression and/or anxiety disorders are often prescribed selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), which, when still in the infant's circulatory system, can cause clinical signs that lead to a diagnosis of NAS (Grigoriadis et al., 2013). Together these two classes of drugs are known as SRIs. In a study of >200,000 pregnant women taking a prescription opioid, the concurrent use of antidepressants, gabapentin, benzodiazepines, and antipsychotics increased the frequency and severity of NOWS (Huybrechts et al., 2017). The specific role of SRIs in exacerbating NAS was shown in a study comparing NOWS severity between neonates born to opioid using mothers who also used SRIs with a control group who did not use SRIs (Bakhireva et al., 2021) and found that neonates of mothers in the SRI group were more likely to need pharmacological treatment and had a longer length of stay. These findings invite speculation about mechanisms involved in these effects, like drug-to-drug interactions between SRIs and opioid medications that inhibit the reuptake of serotonin.

Although drug-to-drug interactions likely play an important role, other potential mechanisms should be considered. First, a serotonin toxicity syndrome has been described that includes signs like NAS including irritability, hypertonia, and tremors

(Grigoriadis et al., 2013). Neurobehavioral assessment comparing SRI exposure – in addition to other substances – with unexposed neonates shows worse performance in the SRI-exposed group across several domains of function that persist throughout the first month (Salisbury et al., 2016). This assessment was performed with the NICU Network Neurobehavioral Scales (NNNS) which provides a standardized evaluation of the presence or absence of the motor and behavioral signs used in the assessment of NAS, as well as the severity and frequency of these signs (Lester & Tronick, 2004). Critically, neurobehavioral profiles using the NNNS predicted developmental outcome in neonates with NAS and infant medical and behavioral outcomes through early childhood in children with cocaine and/or opioid exposure (Flanery et al., 2020; Liu et al., 2010). Thus, SRI exposure could have an additive rather than drug-to-drug interaction effect. This would mean that NOWS scores that meet criteria for pharmacological treatment in infants with SRI and opiate exposure could be artificially inflated resulting in neonates receiving pharmacologic treatment with an opioid when it is not warranted.

In addition, biologic mechanisms associated with psychiatric disorders could similarly affect neonatal neurobehavior independent of prenatal SRI or opioid exposure (i.e., depressed women who are not treated with pharmacologic therapy). For example, maternal depression is associated with immune dysregulation, increased inflammation, and stress-related alterations in the hypothalamic–pituitary axis (HPA), resulting in increasing cortisol levels (Haapakoski et al., 2015; Leff-Gelman et al., 2016; Seth et al., 2016). Increased cortisol levels can be related to increased maternal and neonatal stress and influence the severity of NOWS. In a study examining salivary cortisol levels and NOWS severity, cortisol levels were higher in the first week of life and did not fall in neonates requiring pharmacologic treatment for NAS compared to those who did not require treatment (Rodriguez et al., 2020).

The neurobehavioral assessment of neonates born to mothers with untreated depression as well as neonates of mothers who were prescribed SRIs during pregnancy showed a flatter trajectory and a widening gap in neurobehavioral performance compared to unexposed controls (Salisbury et al., 2016). Maternal depression could directly result in programming of fetal/neonatal neurobehavior through epigenetic changes in placental genes implicated in perturbations of the HPA axis. Neonates of mothers with depression had greater methylation of placental *NR3C1* and showed worse neurobehavioral performance that could have resulted from chronically increased levels of corticosteroids *in utero* (Conradt et al., 2013). From a fetal programming perspective, these epigenetic changes could occur due to adjustments in neurobehavioral systems in response to maternal “signals” transmitted to the fetus

(Gluckman et al., 2008). From a prevention perspective, maternal mindfulness was related to neonatal neurobehavior in mothers with emotional dysregulation during pregnancy, likely due to the impact of stress reduction on the HPA axis (Ostlund et al., 2021). Stress reduction techniques (e.g., nonpharmacologic care) could have similar effects on neonates with or without prenatal opioid exposure, thereby reducing NAS severity and the need for pharmacologic treatment.

The impact of polysubstance exposure on NOWS severity has serious implications for the general approach and pharmacologic management of NOWS (Bakhireva et al., 2021). On the one hand, it is possible that nonopioid drugs can “truly” increase NOWS severity. On the other hand, there is the specter that assessment tools and severity scores (designed specifically to assess opioid withdrawal) could be inflated by the presence of other substances potentially leading to the unwarranted use of pharmacologic treatment. Clearly, there is an urgent need to better identify neonates at risk for NOWS and develop novel approaches for prevention and treatment.

Long-term neurodevelopmental outcome for children with prenatal opioid exposure

Children prenatally exposed to opioids often have long-term disruptions in cognitive, behavioral, and perceptual development (Conradt et al., 2019). Although there are mixed findings for cognitive outcomes, slightly lower cognitive capabilities, including IQ and motor scores (Levine et al., 2021), and neurologic and language performances (Kim et al., 2021) have been linked to prenatal opioid exposure. Moreover, childhood disruptions in executive functioning, such as information processing and vigilance, are associated with prenatal opioid exposure; however, no differences have been found for short-term memory or inhibition. Behavioral and emotional difficulties for children prenatally exposed to opioids appear more consistent (Jaekel et al., 2021), with elevated aggression, fear, and anxiety, as well as heightened indicators of attention-deficit/hyperactivity disorder and lower levels of attention. The few studies examining perceptual differences suggest that opioid-exposed children may have lower visual-motor and perceptual performance scores than their unexposed peers. Furthermore, children diagnosed with NOWS have poorer neurodevelopmental outcomes compared with children exposed to opioids who were not diagnosed. These children are more likely to have developmental delays, lower IQ and attention, and poorer educational performances, as well as more likely to be admitted to a neuropsychiatric disorder, to meet criteria for a disability, and to require classroom services compared to children without a NOWS diagnosis and unexposed peers.

However, much of the literature on the long-term outcomes associated with prenatal opioid exposure is limited due to retrospective chart reviews, small sample sizes, and unaccounted for confounding variables, including prenatal exposure to other substances, inadequate prenatal nutrition and care, medical complications, socioeconomic status, quality of the postnatal environment, maternal mental health and trauma exposure, and substance use of the partner, all of which are related to opioid use and disrupted child development. Recent literature found that postnatal and family factors accounted for approximately half of the differences in opioid exposed and nonexposed children’s cognitive and motor outcomes (Levine et al., 2021). Further, resilience factors such as quality of parenting and the home environment, as well as participation in preschool positively mediated the relationship between prenatal opioid exposure and child language outcomes (Kim et al., 2021). Therefore, when investigating long-term outcomes associated with maternal opioid use disorder, considerations should be made for biopsychosocial risk and resilience factors in the child–caregiver dyad (Jaekel et al., 2021). To this end, the NIH HEALTHY Brain and Child Development Study (HEAL) was developed to more rigorously assess the impact of prenatal opioid exposure on child developmental outcomes and to identify resilience and protective factors that may reduce child morbidity.

Conclusions

Prenatal exposures affect health across two generations: the pregnant woman and the child. We have highlighted how liability for substance use in the pregnant person may emerge, reviewed the pathophysiology of prenatal opioid exposure, and described factors associated with the development and treatment of NOWS. In the United States, there are significant gaps in quality of care for newborns with prenatal substance exposure both during hospitalization and following hospital discharge. A diagnosis of NOWS, for instance, does not lead to automatic qualification for early intervention in many states. This lack of postnatal care for the infant and caregivers is a significant concern given that postnatal factors, such as sensitive caregiving, and nurse–family partnerships to provide tangible and emotional supports to families affected by opioid use, can buffer children against the effects of early life stress. In response to this need for early intervention, neuroscience-informed prevention programs for children exposed to opioids are being developed to prevent intergenerational effects of substance abuse. These kinds of programs are important because they will be needed long after the current opioid epidemic ends. Epidemics tend to occur in cycles – from prenatal cocaine exposure in the 1990s, to methamphetamine in the early

2000s to the opioid crisis today. Policies and interventions that are put into practice now could therefore be updated for the next drug epidemic to mitigate the risks associated with prenatal substance exposure.

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Key points

- The neurodevelopmental consequences of prenatal opioid exposure have typically been studied by examining child-only effects. A lack of attention has been paid toward understanding how these neurodevelopmental outcomes have prenatal and even preconception origins.
- We summarize for the clinician the mechanisms by which prenatal opioid exposure can impact neurodevelopment, with the understanding that many of these mechanisms are perpetuated across generations.
- We discuss the importance of targeting these mechanisms for early intervention to disrupt intergenerational transmission of risk for neurodevelopmental challenges.

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